(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 217 000 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
26.06.2002 Bulletin 2002/26

(21) Application number: **00128477.7**

(22) Date of filing: **23.12.2000**

(51) Int Cl.[7]: **C07D 401/00**, C07D 213/30, C07D 333/16, C07D 333/58, A61K 31/38, A61K 31/435

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
Designated Extension States:
AL LT LV MK RO SI

(71) Applicant: **Aventis Pharma Deutschland GmbH**
65929 Frankfurt am Main (DE)

(72) Inventors:
- **Nazaré, Marc, Dr.**
  65817 Eppstein (DE)
- **Will, David William, Dr.**
  65830 Kriftel (DE)
- **Peyman, Anuschirwan, Dr.**
  65779 Kelkheim (DE)
- **Matter, Hans, Dr.**
  63505 Langenselbold (DE)
- **Zoller, Gerhard, Dr.**
  61137 Schöneck (DE)
- **Gerlach, Uwe, Dr.**
  65795 Hattersheim (DE)

(54) Inhibitors of factor Xa and factor VIIa

(57) The present invention relates to compounds of the formula I,

$$R^0\text{-}Q\text{-}X\text{-}Q'\text{-}W\text{-}U\text{-}V\text{-}G\text{-}M \qquad (I)$$

in which Q; X; Q', U, V, G and M have the meanings indicated in the claims; R^0 is aryl or heteroaryl; and W is selected from aryl, heteroaryl, carbocyclic and heterocyclic groups. The compounds of the formula I are valuable pharmacologically active compounds. They exhibit a strong antithrombotic effect and are suitable, for example, for the therapy and prophylaxis of cardiovascular disorders like thromboembolic diseases or restenoses. They are reversible inhibitors of the blood clotting enzymes factor Xa(FXa) and/or factor VIIa(FVIIa), and can in general be applied in conditions in which an undesired activity of factor Xa and/or factor VIIa is present or for the cure or prevention of which an inhibition of factor Xa and/or factor VIIa is intended. The invention furthermore relates to processes for the preparation of compounds of the formula I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical preparations comprising them.

EP 1 217 000 A1

Description

[0001] The present invention relates to compounds of the formula I,

$$R^0\text{-}Q\text{-}X\text{-}Q'\text{-}W\text{-}U\text{-}V\text{-}G\text{-}M \quad (I)$$

in which R^0 ; Q; X; Q', W ;U, V, G, M have the meanings indicated below. The compounds of the formula I are valuable pharmacologically active compounds. They exhibit a strong antithrombotic effect and are suitable, for example, for the therapy and prophylaxis of cardiovascular disorders like thromboembolic diseases or restenoses. They are reversible inhibitors of the blood clotting enzymes factor Xa (FXa) and/or factor VIIa (FVIIa), and can in general be applied in conditions in which an undesired activity of factor Xa and/or factor VIIa is present or for the cure or prevention of which an inhibition of factor Xa and/or factor VIIa is intended. The invention furthermore relates to processes for the preparation of compounds of the formula I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical preparations comprising them.

[0002] Normal haemeostasis is the result of a complex balance between the processes of clot initiation, formation and clot dissolution. The complex interactions between blood cells, specific plasma proteins and the vascular surface, maintain the fluidity of blood unless injury and blood loss occurs (EP-A-987274). Many significant disease states are related to abnormal haemostasis. For example, local thrombus formation due to rupture of atheroslerotic plaque is a major cause of acute myocardial infarction and unstable angina. Treatment of an occlusive coronary thrombus by either thrombolytic therapy or percutaneous angioplasty may be accompanied by acute thrombolytic reclosure of the affected vessel.

[0003] There continues to be a need for safe and effective therapeutic anticoagulants to limit or prevent thrombus formation. It is most desirable to develop agents that inhibit coagulation without directly inhibiting thrombin but by inhibiting other steps in the coagulation cascade like factor Xa and/or factor VIIa activity. It is now believed that inhibitors of factor Xa carry a lower bleeding risk than thrombin inhibitors (A. E. P. Adang & J. B. M. Rewinkel, Drugs of the Future 2000, 25, 369-383).

[0004] Low molecular weight, factor Xa-specific blood clotting inhibitors that are effective but do not cause unwanted side effects have been described, for example, in WO-A-95/29189. However, besides being an effective factor Xa-specific blood clotting inhibitor, it is desirable that such inhibitors also have further advantageous properties, for instance stability in plasma and liver and selectivity versus other serine proteases whose inhibition is not intended, such as thrombin. There is an ongoing need for further low molecular weight factor Xa specific blood clotting inhibitors which are effective and have the above-advantages as well.

[0005] Specific inhibition of the factor VIIa/tissue factor catalytic complex using monoclonal antibodies (WO-A-92/06711) or a protein such as chloromethyl ketone inactivated factor VIIa (WO-A-96/12800, WO-A-97/47651) is an extremely effective means of controlling thrombus formation caused by acute arterial injury or the thrombotic complications related to bacterial septicemia. There is also experimental evidence suggesting that inhibition of factor VIIa/tissue factor activity inhibits restenosis following balloon angioplasty. Bleeding studies have been conducted in baboons and indicate that inhibition of the factor VIIa/tissue factor complex has the widest safety window with respect to therapeutic effectiveness and bleeding risk of any anticoagulant approach tested including thrombin, platelet and factor Xa inhibition. Certain inhibitors of factor VIIa have already been described. EP-A-987274, for example discloses compounds containing a tripeptide unit which inhibit factor VIIa. However, the property profile of these compounds is still not ideal, and there is an ongoing need for further low molecular weight factor VIIa inhibitory blood clotting inhibitors.

[0006] The present invention satisfies the above needs by providing novel compounds of the formula I which exhibit factor Xa and/or factor VIIa inhibitory activity and are favorable agents for inhibiting unwanted blood clotting and thrombus formation.

[0007] I) Thus, the present invention relates to compounds of the formula I,

$$R^0\text{-}Q\text{-}X\text{-}Q'\text{-}W\text{-}U\text{-}V\text{-}G\text{-}M \quad (I)$$

wherein

R^0 is

1. a monocyclic or bicyclic 5- to 14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2, or
2. a monocyclic or bicyclic 5- to 14-membered heteroaryl, containing zero, one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein heteroaryl is unsubstituted or mono-,

di- or trisubstituted independently of one another by R^2,

R^2 is halogen, $-NO_2$, -CN, $-C(O)-NH_2$, -OH, $-NH_2$, $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue, or $-(C_1-C_8)$-alkyloxy, wherein alkyloxy is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,

Q and Q' are independently of one another identical or different and are a direct bond, -C(O)-; -O-, -S-, $-NR^{10}$-, $-C(O)-NR^{10}$-, $-NR^{10}-C(O)$-, -S(O)-, $-SO_2$-, $-NR^{10}-SO_2$-, $-SO_2-NR^{10}$-, $-(C_1-C_6)$-alkylen, wherein alkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2 or -OH; or $-(C_3-C_6)$-cycloalkylen, wherein cycloalkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, $-NH_2$ or -OH;

X is a direct bond, a 3- to 7-membered heteroaryl, $-(C_1-C_6)$-alkylen, wherein alkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, $-NH_2$ or -OH; or $-(C_3-C_6)$-cycloalkylen, wherein cycloalkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, $-NH_2$ or -OH; provided that when Q or Q' is $-(C_1-C_6)$-alkylen then X is -O-, -S-, $-NR^{10}$-, -C(O)-, $-C(O)-NR^{10}$-, $-NR^{10}-C(O)$-, -S(O)-, $-SO_2$-, $-NR^{10}-SO_2$- or $-SO_2-NR^{10}$-;

with the proviso that if X is a direct bond, the fragment -Q -X- Q'- is not O-O, O-S, S-O, S-S, SO_2-SO_2, SO-SO, $SO-SO_2$, SO_2-SO, SO_2-S, $S-SO_2$, SO-S, S-SO;
with the proviso that if X is oxygen atom or sulfur atom, then Q and Q' are not oxygen atom or sulfur atom; and
with the further proviso that if X is S(O) or SO_2, then Q and Q' are not oxygen atom or sulfur atom;

W is
1. a 5- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,
2. a 5- to14-membered heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,
3. a 4-to 15 membered mono- or polycyclic group, wherein said mono- or polycyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1, or
4. a 4-to 15 membered mono- or polycyclic group, containing one, two, three or four heteroatoms, such as nitrogen, sulfur or oxygen, wherein said mono- or polycyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

provided that if W is a six membered aryl or heteroaryl group, then Q' and U are not in an ortho position with respect to each other;

R^1 is
1. halogen,
2. $-NO_2$,
3. -CN,
4. $-NH_2$,
5. (C_1-C_8)-alkylamino-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
6. -OH,
7. $-SO_2-NH_2$,
8. (C_1-C_8)-alkyloxy-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
9. (C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
10 (C_1-C_8)-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
11. hydroxycarbonyl-(C_1-C_8)-alkylureido-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
12. (C_1-C_8)-alkyloxycarbonyl-(C_1-C_8)-alkylureido-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
13. (C_1-C_8)-alkylsulfonyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
14. bis[(C_1-C_8)-alkyl]amino, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently

of one another by R^{13},
15. $-C(O)-NH_2$,
16. -COOH;
17. $-C(O)-(C_1-C_6)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
18. $-C(O)-O-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
19. $-C(O)-NR^{11}R^{12}$,
20. $-C(O)-NH-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
21. $-C(O)-NH-[(C_1-C_8)\text{-alkyl}]_2$, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
22. $-C(NH)-NH_2$,
23. ureido,
24. $-(C_1-C_8)$-alkylthio, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, or
25. $R^{11}R^{12}N$-, or

two R^1 residues bonded to adjacent ring carbon atoms together with the carbon atoms to which they are bonded form an aromatic ring condensed to W, where the ring formed by the two R^1 residues is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

R^{11} and R^{12} together with the nitrogen atom to which they are bonded form a saturated or unsaturated 5- to 6-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^{11} and R^{12} can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen, and in which one or two of the ring carbon atoms can be substituted by oxo to form -C(O)- residue(s),

R^{13} is halogen, $-NO_2$, -CN, -OH, $-(C_1-C_8)$-alkyl, $-(C_1-C_8)$-alkyloxy, $-CF_3$, $-C(O)-NH_2$ or $-NH_2$,

R^{10} is hydrogen atom or $-(C_1-C_4)$-alkyl,

U and G are independently of one another identical or different and are a direct bond, $-(CH_2)_m$, $-(CH_2)_m-O-(CH_2)_n$-, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n$, $-(CH_2)-SO_2-(CH_2)_n$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n$, $-(CH_2)_m-C(O)-(CH_2)_n$, $-(CH_2)-S-(CH_2)_n$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n$, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n$, $-(CH_2)_m-CH(OH)-(CH_2)_n$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n$ or $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n$,

n and m are are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6, wherein the alkylen residues are unsubstituted or mono-, di- or trisubstituted independently of one another by $-(C_1-C_4)$-alkyl; -C(O)-OH, $-C(O)-O-(C_1-C_4)$-alkyl, $-C(O)-NR^4R^5$, $-SO_2$, $-NR^4R^5$ or $-(C_1-C_8)$-alkylsulfonyl,

R^4 and R^5 are independently of one another identical or different and are hydrogen atom, $-(C_1-C_6)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-(C_6-C_{14})$-aryl-(C_1-C_4)-alkyl-, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, $-(C_6-C_{14})$-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-(C_6-C_{14})$-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} or $-(C_6-C_{14})$-heteroaryl-(C_1-C_4)-alkyl-, wherein alkyl and heteroaryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, or

R^4 and R^5 together with the nitrogen atom to which they are bonded form a saturated 5- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^4 and R^5 can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

V is
1. a direct bond,
2. $-(C_1-C_6)$-alkylen, which is branched or unbranched and which is unsubstituted or mono-, di- or trisubstituted independently of one another
by halogen, =O, -CN, -OH, $-NR^4R^5$, -C(O)-OH, $-C(O)-O-(C_1-C_4)$-alkyl, $-SO_2-NR^4R^5$, $-C(O)-NR^4R^5$ or $-(C_1-C_8)$-alkylsulfonyl,
3. a 3- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
4. a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently

of one another by R^{14}, or
5. a heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

R^{14} is halogen, -OH, $-NR^4R^5$, =O, $-(C_1-C_4)$-alkyl, $-(C_1-C_4)$-alkoxy, $-NO_2$, -C(O)-OH, -CN, $-C(O)-O-(C_1-C_4)$-alkyl, $-C(O)-NR^4R^5$, $-(C_1-C_8)$-alkylsulfonyl, $-C(O)-NR^4R^5$, $-SO_2$, $-C(O)-NH-(C_1-C_8)$-alkyl, $-C(O)-NH-[(C_1-C_8)\text{-alkyl}]_2$, $-NR^{10}-C(O)-NH-(C_1-C_8)$-alkyl, $-C(O)-NH_2$, $-SO_2-NR^4R^5$, $-SR^4$, or $-NR^{10}-C(O)-NH-[(C_1-C_8)\text{-alkyl}]_2$, wherein R^4, R^5 and R^{10} are as defined above, and

M is
1. a hydrogen atom,
2. $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
3. $-C(O)-NR^4R^5$,
4. $-(C_6-C_{14})$-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
5. $-(C_6-C_{14})$-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
6. a 3- to 7-membered cyclic group, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
7. a 3- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, wherein R^{14} is defined above,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

[0008] II) Preferred are compounds of the formula I, wherein

R^0 is phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2,

pyridyl, wherein pyridyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2,
pyrimidyl, wherein pyrimidyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2, or
naphthyl, wherein naphthyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2,

R^2 is as defined above and wherein the alkyl- or alkyloxy residue is unsubstituted or mono-, di- or trisubstituted independently of one another by an amino residue or a methoxy residue,

Q and Q' are as defined above and wherein the alkylen- or cycloalkylen residue is unsubstituted or mono-, di- or trisubstituted independently of one another by $-NH_2$ or -OH;

X is is as defined above,

W is phenyl, pyridyl, pyrimidyl, benzoxazole, benzthiazole, indole, benzo[1,3]dioxole, or naphthyl, wherein W is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

provided that if W is a six membered aryl or heteroaryl group, Q' and U are not in an ortho position with respect to each other;

R^1, R^{10}, R^{11}, R^{12} and R^{13} are as defined above,

U and G are independently of one another identical or different and are a direct bond, $-(CH_2)_m$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n$, $-(CH_2)_m-C(O)-(CH_2)_n$, $-(CH_2)-S-(CH_2)_n$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n$, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n$ or $-(CH_2)_m-CH(OH)-(CH_2)_n$,
wherein n, m, R^4 and R^5 are as defined above,

V and M are as defined above,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

[0009] III) Especially preferred are compounds of the formula I, wherein

R^0 is phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another

by R^2,

pyridyl, wherein pyridyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2,
pyrimidyl, wherein pyrimidyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2, or
naphthyl, wherein naphthyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2,

R^2 is halogen, -CN, $-NH_2$, $-C(O)-NH_2$, $-(C_1-C_4)$-alkyl, or $-(C_1-C_4)$-alkyloxy, wherein the alkyl- or alkyloxy residue is unsubstituted or mono-, di- or trisubstituted independently of one another by an amino residue or a methoxy residue,

Q and Q' are independently of one another identical or different and are a direct bond, -C(O)-; -O-, $-NR^{10}$-, -C(O)$-NR^{10}$-, $-NR^{10}$-C(O)-, $-SO_2$-, $-NR^{10}-SO_2$-, $-SO_2-NR^{10}$-, $-(C_1-C_4)$-alkylen, wherein alkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen; or $-(C_3-C_6)$-cycloalkylen, wherein cycloalkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen;

X is a direct bond, $-(C_1-C_3)$-alkylen, wherein alkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen; or
$-(C_3-C_6)$-cycloalkylen, wherein cycloalkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen;
provided that when Q or Q' is $-(C_1-C_3)$-alkylen then X is -O-, $-NR^{10}$-, -C(O)-, -C(O)$-NR^{10}$-, $-NR^{10}$-C(O)-, $-SO_2$-, $-NR^{10}-SO_2$- or $-SO_2-NR^{10}$-;
with the proviso that if X is a direct bond, the fragment -Q-X-Q'- is not O-O, SO_2-SO_2, or SO-SO_2; and
with the proviso that if X is oxygen atom, then Q and Q' are not oxygen atom or sulfur atom; and
with the further proviso that if X is SO_2, then Q and Q' are not oxygen atom or sulfur atom;

W is phenyl, pyridyl, pyrimidyl, benzoxazole, benzthiazole, indole, benzo[1,3]dioxole, or naphthyl, wherein W is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

provided that if W is a six membered aryl or heteroaryl group, Q' and U are not in an ortho position with respect to each other;

R^1 is
1. halogen,
2. $-NO_2$,
3. -CN,
4. NH_2,
5. (C_1-C_6)-alkylamino-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
6.-OH,
7.$-SO_2-NH_2$,
8. (C_1-C_6)-alkyloxy-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
9.(C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
10 (C_1-C_6)-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
11. hydroxycarbonyl-(C_1-C_6)-alkylureido-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
12. (C_1-C_6)-alkyloxycarbonyl-(C_1-C_6)-alkylureido-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
13. (C_1-C_6)-alkylsulfonyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
14. [(C_1-C_6)-alkyl]amino, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
15. $-C(O)-NH_2$,
16. -C(O)-OH,
17. $-C(O)-(C_1-C_6)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

	18. -C(O)-NH-(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
	19.-C(O)-NH-[(C_1-C_6)-alkyl]$_2$, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
	20. -C(NH)-NH_2,
	21. ureido,
	22. -(C_1-C_6)-alkylthio, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, or
	23. $R^{11}R^{12}N$-, or
two R^1	residues bonded to adjacent ring carbon atoms together with the carbon atoms to which they are bonded form an aromatic ring condensed to W, where the ring formed by the two R^1 residues is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
R^{11} and R^{12}	together with the nitrogen atom to which they are bonded form a saturated or unsaturated 5- to 6-membered monocyclic heterocyclic ring which in addition to the.nitrogen atom carrying R^{11} and R^{12} can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen, and in which one or two of the ring carbon atoms can be substituted by oxo to form -C(O)-residue(s),
R^{13} is	halogen, -CN, -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyloxy, -CF_3, -C(O)-NH_2 or -NH_2,
R^{10} is	hydrogen atom or -(C_1-C_4)-alkyl,
U and G are	independently of one another identical or different and are a direct bond, -$(CH_2)_m$, -$(CH_2)_m$-O-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-NR^{10} -$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$, -$(CH_2)_m$-C(O)-$(CH_2)_n$, -(CH_2)-S-$(CH_2)_n$, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$, or -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$,
n and m are	are independently of one another identical or different and are the integers zero, 1, 2 or 3, wherein the alkylen residues are unsubstituted or mono-, di- or trisubstituted independently of one another by -(C_1-C_4)-alkyl; -C(O)-OH, -C(O)-O-(C_1-C_4)-alkyl, -C(O)-NR^4R^5, -SO_2, -NR^4R^5 or -(C_1-C_8)-alkylsulfonyl,
R^4 and R^5 are	independently of one another identical or different and are hydrogen atom, -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -(C_6-C_{14})-aryl-(C_1-C_4)-alkyl-, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, -(C_6-C_{14})-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -(C_6-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} or -(C_6-C_{14})-heteroaryl-(C_1-C_4)-alkyl-, wherein alkyl and heteroaryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, or
R^4 and R^5	together with the nitrogen atom to which they are bonded form a saturated 5- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^4 and R^5 can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
V is	1. a direct bond,
	2. -(C_1-C_4)-alkylen, which is branched or unbranched and which is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, =O, -CN, -OH, -NR^4R^5, -C(O)-OH, -C(O)-O-(C_1-C_4)-alkyl, -SO_2, -NR^4R^5, -C(O)-NR^4R^5 or -(C_1-C_8)-alkylsulfonyl,
	3. a 5- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
	4. a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
	5. a heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
R^{14} is	halogen, -OH, -NR^4R^5, =O, -(C_1-C_4)-alkyl, -(C_1-C_4)-alkoxy, -NO_2, -C(O)-OH, -CN, -C(O)-O-(C_1-C_4)-alkyl, -C(O)-NR^4R^5, -(C_1-C_8)-alkylsulfonyl, -C(O)-NR^4R^5, -SO_2-NR^4R^5, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH-[(C_1-C_8)-alkyl]$_2$, -NR^{10}-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH_2 or -NR^{10}-C(O)-NH-[(C_1-C_8)-alkyl]$_2$, wherein R^4, R^5 and R^{10} are as defined above, and
M is	1. a hydrogen atom,
	2. -(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one

another by R^{14},
3. -C(O)-NR^4R^5,
4. -(C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
5. -(C_6-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
6. a 5- to 7-membered cyclic group, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
7. a 5- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, wherein R^{14} is defined above.

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

[0010] IV) Further preferred are compounds of the formula I, wherein

R^0 is phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2, or

pyridyl, wherein pyridyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2,

R^2 is halogen, -CN, -C(O)-NH_2, -(C_1-C_4)-alkyl, or -(C_1-C_4)-alkyloxy, wherein the alkyl- or alkyloxy residue is unsubstituted or mono-, di- or trisubstituted independently of one another by an amino residue or a methoxy residue,

Q and Q' are independently of one another identical or different and are a direct bond, -C(O)-; -O-, -NR^{10}-, -C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, -NR^{10}-SO_2-, -SO_2-NR^{10}-, or -(C_1-C_4)-alkylen,

X is a direct bond or -(C_1-C_3)-alkylen,
provided that when Q or Q' is -(C_1-C_3)-alkylen then X is -O-, -NR^{10}-, -C(O)-, -C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, -NR^{10}-SO_2- or -SO_2-NR^{10}-;

with the proviso that if X is a direct bond, the fragment -Q -X- Q'- is not O-O or SO_2-SO_2;
and with the proviso that if X is oxygen atom, then Q and Q' are not oxygen atom or sulfur atom; and
with the further proviso that if X is SO_2, then Q and Q' are not oxygen atom or sulfur atom;

W is phenyl, pyridyl or pyrimidyl, wherein W is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

provided that Q' and U are not in an ortho position with respect to each other;

R^1 is
1. halogen,
2. -NO_2,
3. -CN,
4. -NH_2,
5. (C_1-C_4)-alkylamino-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
6. -OH,
7. -SO_2-NH_2,
8. (C_1-C_4)-alkyloxy-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
9. (C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
10. (C_1-C_4)-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
11. hydroxycarbonyl-(C_1-C_4)-alkylureido-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
12. (C_1-C_4)-alkyloxycarbonyl-(C_1-C_4)-alkylureido-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
13. (C_1-C_4)-alkylsulfonyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

14. bis[(C_1-C_4)-alkyl]amino, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
15. -C(O)-NH_2,
16. -C(O)-OH,
17. -C(O)-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
18. -C(O)-NH-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
19. -C(O)-NH-[(C_1-C_4)-alkyl]$_2$, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
20. -C(NH)-NH_2,
21. ureido,
22. -(C_1-C_4)-alkylthio, wherein alkylthio is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, or
23. $R^{11}R^{12}N$-, or

two R^1 residues bonded to adjacent ring carbon atoms together with the carbon atoms to which they are bonded form an aromatic ring condensed to W, where the ring formed by the two R^1 residues is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

R^{11} and R^{12} together with the nitrogen atom to which they are bonded form a saturated or unsaturated 5- to 6-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^{11} and R^{12} can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen,

R^{13} is halogen, -CN, -(C_1-C_4)-alkyl, -(C_1-C_4)-alkyloxy, -CF_3, -C(O)-NH_2 or -NH_2,

R^{10} is hydrogen atom or -(C_1-C_4)-alkyl,

U and G are independently of one another identical or different and are a direct bond, -$(CH_2)_m$-, -$(CH_2)_m$-C(O)-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$-, or -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$-,

n and m are are independently of one another identical or different and are the integers zero, 1, 2 or 3, wherein the alkylen residues are unsubstituted or mono-, di- or trisubstituted independently of one another by -(C_1-C_4)-alkyl; -C(O)-OH, -C(O)-O-(C_1-C_4)-alkyl or -C(O)-NR^4R^5,

R^4 and R^5 are independently of one another identical or different and are hydrogen atom, -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -(C_6-C_{14})-aryl-(C_1-C_4)-alkyl-, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, -(C_6-C_{14})-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -(C_6-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} or -(C_6-C_{14})-heteroaryl-(C_1-C_4)-alkyl-, wherein alkyl and heteroaryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, or

R^4 and R^5 together with the nitrogen atom to which they are bonded form a saturated 5- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^4 and R^5 can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

V is
1. a direct bond,
2. -(C_1-C_4)-alkylen, which is branched or unbranched and which is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, =O, -CN, -OH, -NR^4R^5, -C(O)-OH, -C(O)-O-(C_1-C_4)-alkyl, -SO_2-NR^4R^5, -C(O)-NR^4R^5 or -(C_1-C_4)-alkylsulfonyl,
3. a 5- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
4. a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
5. a 6- to14-membered heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

R^{14} is halogen, -OH, -NR^4R^5, =O, -(C_1-C_4)-alkyl, -(C_1-C_4)-alkoxy, -NO_2, -C(O)-OH, -CN, -C(O)-O-(C_1-C_4)-alkyl, -C(O)-NR^4R^5, -(C_1-C_8)-alkylsulfonyl, -C(O)-NR^4R^5, -SO_2-NR^4R^5, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH-[(C_1-C_8)-alkyl]$_2$, -NR^{10}-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH_2 or -NR^{10}-C(O)-NH-[(C_1-C_8)-alkyl]$_2$, wherein R^4, R^5 and R^{10} are as defined above, and

M is
1. a hydrogen atom,
2. -(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
3. -C(O)-NR^4R^5,
4. -(C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
5. -(C_6-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
6. a 5- to 7-membered cyclic group, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
7. a 5- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, wherein R^{14} is defined above,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

[0011] V) Further especially preferred are compounds of the formula I, wherein

R^0 is phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R^2, or

pyridyl, wherein pyridyl is unsubstituted or mono-, disubstituted independently of one another by R^2,

R^2 is halogen, -CN, -C(O)-NH_2, -(C_1-C_3)-alkyl, or -(C_1-C_3)-alkyloxy, wherein the alkyl- or alkyloxy residue is unsubstituted or mono-, di- or trisubstituted independently of one another by an amino residue or a methoxy residue,

Q and Q' are independently of one another identical or different and are a direct bond, -C(O)-; -O-, -NR^{10}-, -C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, -NR^{10}-SO_2-, -SO_2-NR^{10}-, or -(C_1-C_4)-alkylen,

X is a direct bond or -(C_1-C_3)-alkylen,
provided that when Q or Q' is -(C_1-C_3)-alkylen then X is -O-, -NR^{10}-, -C(O)-, -C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, -NR^{10}-SO_2- or -SO_2-NR^{10}-;
with the proviso that if X is a direct bond, the fragment -Q -X- Q'- is not O-O or SO_2-SO_2; and with the proviso that if X is oxygen atom, then Q and Q' are not oxygen atom or sulfur atom; and
with the further proviso that if X is SO_2, then Q and Q' are not oxygen atom or sulfur atom;

W is phenyl, pyridyl or pyrimidyl, wherein W is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

provided that Q' and U are not in an ortho position with respect to each other;

R^1 is
1. halogen,
2. -NO_2,
3. -CN,
4. -NH_2,
5. (C_1-C_4)-alkylamino-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
6. -OH,
7. -SO_2-NH_2,
8. (C_1-C_4)-alkyloxy-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
9. (C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
10. (C_1-C_4)-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
11. (C_1-C_4)-alkylsulfonyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
12. bis[(C_1-C_4)-alkyl]amino, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
13. -C(O)-NH_2,
14. -C(O)-OH,
15. -C(O)-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently

	of one another by R^{13},
	16. -C(O)-NH-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
	17. -C(O)-NH-[(C_1-C_4)-alkyl]$_2$, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
	18. -C(NH)-NH_2,
	19. ureido,
	20. -(C_1-C_4)-alkylthio, wherein alkylthio is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, or
	21. $R^{11}R^{12}N$-, or
two R^1	residues bonded to adjacent ring carbon atoms together with the carbon atoms to which they are bonded form an aromatic ring condensed to W, where the ring formed by the two R^1 residues is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
R^{11} and R^{12}	together with the nitrogen atom to which they are bonded form a saturated or unsaturated 5- to 6-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^{11} and R^{12} can contain one or two identical or different ring heteroatoms chosen from oxygen or nitrogen,
R^{13} is	halogen, -CN, -(C_1-C_4)-alkyl, -(C_1-C_4)-alkyloxy, -CF_3, -C(O)-NH_2 or -NH_2,
R^{10} is	hydrogen atom or -(C_1-C_4)-alkyl,
U is	a direct bond, -$(CH_2)_m$-, -$(CH_2)_m$-C(O)-NR^{10} -$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$-, or -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$-,
n and m are	are independently of one another identical or different and are the integers zero, 1, 2 or 3, wherein the alkylen residues are unsubstituted or mono-, di- or trisubstituted independently of one another by -(C_1-C_4)-alkyl; -C(O)-OH, -C(O)-O-(C_1-C_4)-alkyl or -C(O)-NR^4R^5,
R^4 and R^5 are	independently of one another identical or different and are hydrogen atom, -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -(C_6-C_{14})-aryl-(C_1-C_4)-alkyl-, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, -(C_6-C_{14})-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -(C_6-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} or -(C_6-C_{14})-heteroaryl-(C_1-C_4)-alkyl-, wherein alkyl and heteroaryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, or
R^4 and R^5	together with the nitrogen atom to which they are bonded form a saturated 5- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^4 and R^5 can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
G is	a direct bond, -$(CH_2)_m$-, -$(CH_2)_m$-O-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-$(CH_2)_n$-, -(CH_2)-S-$(CH_2)_n$-, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$ or -$(CH_2)_m$-SO_2-$(CH_2)_n$-, wherein n, m, and R^{10} are as defined above
V is	1. a direct bond,
	2. -(C_1-C_4)-alkylen, which is branched or unbranched and which is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, =O, -CN, -NR^4R^5, -C(O)-OH, -C(O)-O-(C_1-C_4)-alkyl, -SO_2-NR^4R^5, -C(O)-NR^4R^5 or -(C_1-C_4)-alkylsulfonyl,
	3. a 5- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
	4. a 6- to 14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
	5. a 6- to14-membered heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
R^{14} is	halogen, -OH, -NR^4R^5, =O, -(C_1-C_4)-alkyl, -(C_1-C_4)-alkoxy, -NO_2, -C(O)-OH, -CN, -C(O)-O-(C_1-C_4)-alkyl, -C(O)-NR^4R^5, -(C_1-C_8)-alkylsulfonyl, -C(O)-NR^4R^5, SO_2-NR^4R^5, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH-[(C_1-C_8)-alkyl]$_2$, -NR^{10}-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH_2 or -NR^{10}-C(O)-NH-[(C_1-C_8)-alkyl]$_2$, wherein R^4, R^5 and R^{10} are as defined above, and
M is	1. a hydrogen atom,

2. -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
3. -C(O)-NR^4R^5,
4. -(C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
5. -(C_6-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
6. a 5- to 7-membered cyclic group, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
7. a 5- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, wherein R^{14} is defined above,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

[0012] VI) Further especially preferred are compounds of the formula I, wherein

R^0 is phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R^2, or pyridyl, wherein pyridyl is unsubstituted or mono-, disubstituted independently of one another by R^2,

R^2 is halogen, -CN, -C(O)-NH_2, -(C_1-C_3)-alkyl, or -(C_1-C_3)-alkyloxy, wherein the alkyl- or alkyloxy residue is unsubstituted or mono-, di- or trisubstituted independently of one another by an amino residue or a methoxy residue,

Q and Q' are independently of one another identical or different and are a direct bond, -C(O)-; -O-, -NR^{10}-, -C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, -NR^{10}-SO_2-, -SO_2-NR^{10}-, or -(C_1-C_4)-alkylen,

X is a direct bond or -(C_1-C_3)-alkylen,
provided that when Q or Q' is -(C_1-C_3)-alkylen then X is -O-, -NR^{10}-, -C(O)-, -C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, -NR^{10}-SO_2- or -SO_2-NR^{10}-;

with the proviso that if X is a direct bond, the fragment -Q -X- Q'- is not O-O or SO_2-SO_2;
and with the proviso that if X is oxygen atom, then Q and Q' are not oxygen atom or sulfur atom; and
with the further proviso that if X is SO_2, then Q and Q' are not oxygen atom or sulfur atom;

W is phenyl or pyridyl, wherein W is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

provided that Q' and U are not in an ortho position with respect to each other;

R^1 is
1. halogen,
2. -NO_2,
3. -CN,
4. -NH_2,
5. (C_1-C_4)-alkylamino-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
6. -OH,
7. -SO_2-NH_2,
8. (C_1-C_4)-alkyloxy-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
9. (C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
10. (C_1-C_4)-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
11. (C_1-C_4)-alkylsulfonyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
12. bis[(C_1-C_4)-alkyl]amino, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
13. -C(O)-NH_2,
14. -C(O)-OH,
15. -C(O)-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

16. -C(O)-NH-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
17. -C(O)-NH-[(C_1-C_4)-alkyl]$_2$, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
18. -C(NH)-NH_2,
19. ureido,
20. -(C_1-C_4)-alkylthio, wherein alkylthio is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, or
21. $R^{11}R^{12}N$-, or

two R^1 residues bonded to adjacent ring carbon atoms together with the carbon atoms to which they are bonded form an aromatic ring condensed to W, where the ring formed by the two R^1 residues is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

R^{11} and R^{12} together with the nitrogen atom to which they are bonded form a saturated or unsaturated 5- to 6-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^{11} and R^{12} can contain one or two identical or different ring heteroatoms chosen from oxygen or nitrogen,

R^{13} is halogen, -CN, -(C_1-C_4)-alkyl, -(C_1-C_4)-alkyloxy, $-CF_3$, -C(O)-NH_2 or -NH_2,

R^{10} is hydrogen atom or -(C_1-C_4)-alkyl,

U is a direct bond, -$(CH_2)_m$, -$(CH_2)_m$-C(O)-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$, -$(CH_2)_m$-C(O)-$(CH_2)_n$,-$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$, or -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$,

n and m are are independently of one another identical or different and are the integers zero, 1, 2 or 3, wherein the alkylen residues are unsubstituted or mono-, di- or trisubstituted independently of one another by -(C_1-C_4)-alkyl; -C(O)-OH, -C(O)-O-(C_1-C_4)-alkyl or -C(O)-NR^4R^5,

R^4 and R^5 are independently of one another identical or different and are hydrogen atom, -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -(C_6-C_{14})-aryl-(C_1-C_4)-alkyl-, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, -(C_6-C_{14})-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -(C_6-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} or -(C_6-C_{14})-heteroaryl-(C_1-C_4)-alkyl-, wherein alkyl and heteroaryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, or

R^4 and R^5 together with the nitrogen atom to which they are bonded form a saturated 5- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^4 and R^5 can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

G is a direct bond, -$(CH_2)_m$, -$(CH_2)_m$-O-$(CH_2)_{n-}$, -$(CH_2)_m$-C(O)-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$, -$(CH_2)_m$-C(O)-$(CH_2)_n$, -(CH_2)-S-$(CH_2)_n$, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$, -(CH_2)-S-$(CH_2)_n$, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$ or -$(CH_2)_m$-SO_2-$(CH_2)_n$, -$(CH_2)_m$-NR -SO_2-NR -$(CH_2)_n$ Or -$(CH_2)_m$-SO_2-$(CH_2)_n$,
wherein n, m, and R^{10} are as defined above

V is
1. a direct bond,
2. -(C_1-C_4)-alkylen, which is branched or unbranched and which is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, =O, -CN, -NR^4R^5, -C(O)-OH, -C(O)-O-(C_1-C_4)-alkyl; -SO_2-NR^4R^5, -C(O)-NR^4R^5 or -(C_1-C_4)-alkylsulfonyl,
3. a 5- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
4. a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
5. a 6- to14-membered heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

R^{14} is halogen, -OH, -NR^4R^5, =O, -(C_1-C_4)-alkyl, -(C_1-C_4)-alkoxy, $-NO_2$, -C(O)-OH, -CN, -C(O)-O-(C_1-C_4)-alkyl, -C(O)-NR^4R^5, -(C_1-C_8)-alkylsulfonyl, -C(O)-NR^4R^5, -SO_2-NR^4R^5, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH-[(C_1-C_8)-alkyl]$_2$, -NR^{10}-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH_2 or -NR^{10}-C(O)-NH-[(C_1-C_8)-alkyl]$_2$,
wherein R^4, R^5 and R^{10} are as defined above, and

M is
1. a hydrogen atom,
2. -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
3. -C(O)-NR^4R^5,
4. -(C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
5. -(C_6-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
6. a 5- to 7-membered cyclic group, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
7. a 5- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, wherein R^{14} is defined above,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

[0013] VII) Further especially preferred are compounds of the formula I, wherein

R^0 is phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R^2, or
pyridyl, wherein pyridyl is unsubstituted or mono-, disubstituted independently of one another by R^2,

R^2 is halogen, -CN, -C(O)-NH_2, -(C_1-C_3)-alkyl, or -(C_1-C_3)-alkyloxy, wherein the alkyl- or alkyloxy residue is unsubstituted or mono-, di- or trisubstituted independently of one another by an amino residue or a methoxy residue,

Q and Q' are independently of one another identical or different and are a direct bond, -C(O)-; -O-, -NR^{10}-, -C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, -NR^{10}-SO_2-, -SO_2-NR^{10}-, or -(C_1-C_4)-alkylen,

X is a direct bond or -(C_1-C_3)-alkylen,
provided that when Q or Q' is -(C_1-C_3)-alkylen then X is -O-, -NR^{10}-, -C(O)-, -C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, -NR^{10}-SO_2- or -SO_2-NR^{10}-;

with the proviso that if X is a direct bond, the fragment -Q -X- Q'- is not O-O or SO_2-SO_2;
and with the proviso that if X is oxygen atom, then Q and Q' are not oxygen atom or sulfur atom; and
with the further proviso that if X is SO_2, then Q and Q' are not oxygen atom or sulfur atom;

W is phenyl or pyridyl, wherein W is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

provided that Q' and U are not in an ortho position with respect to each other;

R^1 is
1. halogen,
2. -NO_2,
3. -CN,
4. -NH_2,
5. (C_1-C_4)-alkylamino-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
6. -OH,
7. -SO_2-NH_2,
8. (C_1-C_4)-alkyloxy-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
9. (C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
10. (C_1-C_4)-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
11. (C_1-C_4)-alkylsulfonyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
12. bis[(C_1-C_4)-alkyl]amino, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
13. -C(O)-NH_2,
14. -C(O)-OH,

15. -C(O)-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
16. -C(O)-NH-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
17. -C(O)-NH-[(C_1-C_4)-alkyl]$_2$, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
18. -C(NH)-NH_2,
19. ureido,
20. -(C_1-C_4)-alkylthio, wherein alkylthio is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, or
21. $R^{11}R^{12}N$-, or

two R^1 residues bonded to adjacent ring carbon atoms together with the carbon atoms to which they are bonded form an aromatic ring condensed to W, where the ring formed by the two R^1 residues is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

R^{11} and R^{12} together with the nitrogen atom to which they are bonded form a saturated or unsaturated 5- to 6-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^{11} and R^{12} can contain one or two identical or different ring heteroatoms chosen from oxygen or nitrogen,

R^{13} is halogen, -CN, -(C_1-C_4)-alkyl, -(C_1-C_4)-alkyloxy, $-CF_3$, -C(O)-NH_2 or -NH_2,

R^{10} is hydrogen atom or -(C_1-C_4)-alkyl,

U is -$(CH_2)_m$-C(O)-NR^{10} -$(CH_2)_n$, wherein n and m are independently of one another identical or different and are the integers zero, 1 or 2,

R^4 and R^5 are independently of one another identical or different and are hydrogen atom, -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -(C_6-C_{14})-aryl-(C_1-C_4)-alkyl-, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, -(C_6-C_{14})-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -(C_6-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} or -(C_6-C_{14})-heteroaryl-(C_1-C_4)-alkyl-, wherein alkyl and heteroaryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, or

R^4 and R^5 together with the nitrogen atom to which they are bonded form a saturated 5- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^4 and R^5 can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

G is a direct bond, -$(CH_2)_m$, -$(CH_2)_m$-O-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$, -$(CH_2)_m$-C(O)-$(CH_2)_n$, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$, -$(CH_2)_m$-SO_2-$(CH_2)_n$ or -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$, wherein n, m, and R^{10} are as defined above

V is
1. a 5- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
2. a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
3. a 6- to14-membered heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

R^{14} is halogen, -OH, -NR^4R^5, =O, -(C_1-C_4)-alkyl, -(C_1-C_4)-alkoxy, -NO_2, -C(O)-OH, -CN, -C(O)-O-(C_1-C_4)-alkyl, -C(O)-NR^4R^5, -(C_1-C_8)-alkylsulfonyl, -C(O)-NH_2, -SO_2-NR^4R^5, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH-[(C_1-C_8)-alkyl]$_2$, -NR^{10}-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH_2 or -NR^{10}-C(O)-NH-[(C_1-C_8)-alkyl]$_2$, wherein R^4, R^5 and R^{10} are as defined above, and

M is
1. a hydrogen atom,
2. -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
3. -C(O)-NR^4R^5,
4. -(C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
5. -(C_6-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

6. a 5- to 7-membered cyclic group, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
7. a 5- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, wherein R^{14} is defined above,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

[0014] VIII) More especially preferred are compounds of the formula I, wherein

R^0 is phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R^2, or pyridyl, wherein pyridyl is unsubstituted or mono-, disubstituted independently of one another by R^2,

R^2 is halogen or -CN,
Q is a direct bond
Q' is -O-,
X is $-(C_1-C_3)$-alkylen,
W is phenyl or pyridyl, wherein W is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

provided that Q' and U are not in an ortho position with respect to each other;

R^1 is halogen, $-NO_2$, -CN, $-NH_2$, (C_1-C_4)-alkylamino-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -OH, $-SO_2-NH_2$, (C_1-C_4)-alkyloxy-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, (C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, (C_1-C_4)-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, (C_1-C_4)-alkylsulfonyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, bis$[(C_1-C_4)$-alkyl]amino, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-C(O)-NH_2$, -C(O)-OH, $-C(O)-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-C(O)-NH-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-C(O)-NH-[(C_1-C_4)$-alkyl$]_2$, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-C(NH)-NH_2$, ureido, - (C_1-C_4)-alkylthio, wherein alkylthio is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, or $R^{11}R^{12}N$-, or

two R^1 residues bonded to adjacent ring carbon atoms together with the carbon atoms to which they are bonded form an aromatic ring condensed to W, where the ring formed by the two R^1 residues is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

R^{11} and R^{12} together with the nitrogen atom to which they are bonded form a saturated or unsaturated 5- to 6-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^{11} and R^{12} can contain one or two identical or different ring heteroatoms chosen from oxygen or nitrogen,

R^{13} is halogen, -CN, $-(C_1-C_4)$-alkyl, $-(C_1-C_4)$-alkyloxy, $-CF_3$, $-C(O)-NH_2$ or $-NH_2$,

R^{10} is hydrogen atom or methyl,

U is $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n$, wherein n is zero, 1 or 2, m is zero or 1,

R^4 and R^5 are independently of one another identical or different and are hydrogen atom, $-(C_1-C_6)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-(C_6-C_{14})$-aryl-(C_1-C_4)-alkyl-, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, $-(C_6-C_{14})$-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-(C_6-C_{14})$-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} or $-(C_6-C_{14})$-heteroaryl-(C_1-C_4)-alkyl-, wherein alkyl and heteroaryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, or

R^4 and R^5 together with the nitrogen atom to which they are bonded form a saturated 5- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^4 and R^5 can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

G is a direct bond, $-(CH_2)_m$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n$, $-(CH_2)_m-C(O)-(CH_2)_n$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n$ or $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n$,
wherein n, m, and R^{10} are as defined above

V is
1. a 5- to 6-membered cyclic group, containing up to 1 or 2, heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
2. a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
3. a 6- to14-membered heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

R^{14} is
halogen, -OH, $-NR^4R^5$, =O, $-(C_1-C_4)$-alkyl, $-(C_1-C_4)$-alkoxy, -C(O)-OH, -CN, $-C(O)-O-(C_1-C_4)$-alkyl, $-C(O)-NR^4R^5$, $-(C_1-C_8)$-alkylsulfonyl, $-C(O)-NH_2$, $-SO_2-NR^4R^5$, $-C(O)-NH-(C_1-C_8)$-alkyl, $-C(O)-NH-[(C_1-C_8)\text{-alkyl}]_2$, wherein R^4 or R^5 are as defined above, and

M is
1. a hydrogen atom,
2. $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
3. $-C(O)-NR^4R^5$,
4. $-(C_6-C_{14})$-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
5. $-(C_6-C_{14})$-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
6. a 5- to 6-membered cyclic group, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
7. a 5- to 6-membered cyclic group, containing up to 1 or 2 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, wherein R^{14} is defined above,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

[0015] IX) Even more preferred are compounds of the formula I, wherein

R^0 is phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R^2, or pyridyl, wherein pyridyl is unsubstituted or mono-, disubstituted independently of one another by R^2,

R^2 is chlorine,
Q is a direct bond
Q' is -O-,
X is ethylene,
W is phenyl or pyridyl, wherein W is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

provided that Q' and U are not in an ortho position with respect to each other;

R^1 is
halogen, $-NO_2$, -CN, $-NH_2$, (C_1-C_4)-alkylamino-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -OH, $-SO_2-NH_2$, (C_1-C_4)-alkyloxy-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, (C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, (C_1-C_4)-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, (C_1-C_4)-alkylsulfonyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, bis$[(C_1-C_4)\text{-alkyl}]$amino, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-C(O)-NH_2$, -C(O)-OH, $-C(O)-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-C(O)-NH-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-C(O)-NH-[(C_1-C_4)\text{-alkyl}]_2$, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-C(NH)-NH_2$, ureido, $-(C_1-C_4)$-alkylthio, wherein alkylthio is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, or $R^{11}R^{12}N$-, or

two R^1
residues bonded to adjacent ring carbon atoms together with the carbon atoms to which they are bonded form an aromatic ring condensed to W, where the ring formed by the two R^1 residues is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

R^{11} and R^{12}
together with the nitrogen atom to which they are bonded form a saturated or unsaturated 5- to 6-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^{11} and R^{12} can contain one or two identical or different ring heteroatoms chosen from oxygen or nitrogen,

R^{13} is	halogen, -CN, -(C_1-C_4)-alkyl, -(C_1-C_4)-alkyloxy, -CF_3, -C(O)-NH_2 or -NH_2,
R^{10} is	hydrogen atom or methyl,
U is	-$(CH_2)_m$-C(O)-NR^{10}-$(CH_2)_n$, wherein n is zero, 1 or 2, m is zero or 1,
R^4 and R^5 are	independently of one another identical or different and are hydrogen atom, -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -(C_6-C_{14})-aryl-(C_1-C_4)-alkyl-,

wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, -(C_6-C_{14})-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -(C_6-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} or -(C_6-C_{14})-heteroaryl-(C_1-C_4)-alkyl-, wherein alkyl and heteroaryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, or

R^4 and R^5	together with the nitrogen atom to which they are bonded form a saturated 5- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^4 and R^5 can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
G is	a direct bond, -$(CH_2)_m$, -$(CH_2)_m$-C(O)-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-C(O)-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$ or -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$, wherein n, m, and R^{10} are as defined above
V is	1. a 5- to 6-membered cyclic group, containing up to 1 or 2, heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, 2. a 6-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or 3. a 6-membered heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
R^{14} is	halogen, -OH, -NR^4R^5, =O, -(C_1-C_4)-alkyl, -(C_1-C_4)-alkoxy, -C(O)-OH, -CN, -C(O)-O-(C_1-C_4)-alkyl, -C(O)-NR^4R^5, -(C_1-C_8)-alkylsulfonyl, -C(O)-NH_2, -SO_2-NR^4R^5, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH-[(C_1-C_8)-alkyl]$_2$, wherein R^4 or R^5 are as defined above, and
M is	1. a hydrogen atom, 2. -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, 3. -C(O)-NR^4R^5, 4. -(C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, 5. -(C_6-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, 6. a 5- to 6-membered cyclic group, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or 7. a 5- to 6-membered cyclic group, containing up to 1 or 2 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, wherein R^{14} is defined above,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

[0016] In general, the meaning of any group, residue, heteroatom, number etc. which can occur more than once in the compounds of the formula I, is independent of the meaning of this group, residue, heteroatom, number etc. in any other occurrence. All groups, residues, heteroatoms, numbers etc. which can occur more than once in the compounds of the formula I can be identical or different.

[0017] As used herein, the term alkyl is to be understood in the broadest sense to mean hydrocarbon residues which can be linear, i. e. straight-chain, or branched and which can be acyclic or cyclic residues or comprise any combination of acyclic and cyclic subunits. Further, the term alkyl as used herein expressly includes saturated groups as well as unsaturated groups which latter groups contain one or more, for example one, two or three, double bonds and/or triple bonds, provided that the double bonds are not located within a cyclic alkyl group in such a manner that an aromatic system results. All these statements also apply if an alkyl group occurs as a substituent on another residue, for example in an alkyloxy residue, an alkyloxycarbonyl residue or an arylalkyl residue. Examples of alkyl residues containing 1, 2, 3, 4, 5, 6, 7 or 8carbon atoms are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl or octyl, the n-isomers of all these

residues, isopropyl, isobutyl, 1-methylbutyl, isopentyl, neopentyl, 2,2-dimethylbutyl, 2-methylpentyl, 3-methylpentyl, isohexyl, sec-butyl, tBu, tert-pentyl, sec-butyl, tert-butyl or tert-pentyl.

[0018] Unsaturated alkyl residues are, for example, alkenyl residues such as vinyl, 1-propenyl, 2-propenyl (= allyl), 2-butenyl, 3-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 5-hexenyl or 1,3-pentadienyl, or alkynyl residues such as ethynyl, 1-propynyl, 2-propynyl (= propargyl) or 2-butynyl. Alkyl residues can also be unsaturated when they are substituted.

[0019] Examples of cyclic alkyl residues are cycloalkyl residues containing 3, 4, 5 or 6 ring carbon atoms like cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, which can also be substituted and/or unsaturated. Unsaturated cyclic alkyl groups and unsaturated cycloalkyl groups like, for example, cyclopentenyl or cyclohexenyl can be bonded via any carbon atom.

[0020] Of course, a cyclic alkyl group has to contain at least three carbon atoms, and an unsaturated alkyl group has to contain at least two carbon atoms. Thus, a group like (C_1-C_8)-alkyl is to be understood as comprising, among others, saturated acyclic (C_1-C_8)-alkyl, (C_3-C_6)-cycloalkyl, and unsaturated (C_2-C_8)-alkyl like (C_2-C_8)-alkenyl or (C_2-C_8)-alkynyl. Similarly, a group like (C_1-C_4)-alkyl is to be understood as comprising, among others, saturated acyclic (C_1-C_4)-alkyl, and unsaturated (C_2-C_4)-alkyl like (C_2-C_4)-alkenyl or (C_2-C_4)-alkynyl.

[0021] Unless stated otherwise, the term alkyl preferably comprises acyclic saturated hydrocarbon residues which have from one to six carbon atoms and which can be linear or branched. A particular group of saturated acyclic alkyl residues is formed by (C_1-C_4)-alkyl residues like methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tBu.

[0022] Unless stated otherwise, and irrespective of any specific substituents bonded to alkyl groups which are indicated in the definition of the compounds of the formula I, alkyl groups can in general be unsubstituted or substituted by one or more, for example one, two or three, identical or different substituents. Any kind of substituents present in substituted alkyl residues can be present in any desired position provided that the substitution does not lead to an unstable molecule. Examples of substituted alkyl residues are alkyl residues in which one or more, for example 1, 2 or 3, hydrogen atoms are replaced with halogen atoms, in particular fluorine atoms.

[0023] The term mono- or bicyclic 5- to 14-membered aryl group refers to for example phenyl, biphenyl or napthyl.

[0024] The term mono- or bicyclic 5- to 14-membered heteroaryl refers to (C_5-C_{14})-aryl in which one or more of the 5 to 10 ring carbon atoms are replaced by heteroatoms such as nitrogen, oxygen or sulfur. Examples are pyridyl; such as 2-pyridyl, 3-pyridyl or 4-pyridyl; pyrrolyl; such as 2-pyrrolyl and 3-pyrrolyl; furyl; such as 2-furyl and 3-furyl; thienyl; such as 2-thienyl and 3-thienyl; imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, tetrazolyl, pyridazinyl, pyrazinyl, pyrimidinyl, indolyl, isoindolyl, indazolyl, phthalazinyl, quinolyl, isoquinolyl or quinoxalinyl or phenylpyridyl.

[0025] The term R^{11} and R^{12} together with the nitrogen atom to which they are bonded form a saturated or unsaturated 5- to 6-membered monocyclic heterocyclic ring refers to pyrrol, piperidin, pyrrolidine, morpholine, piperazine, pyridine, pyrimidine, imidazole or thiomorpholine.

[0026] The term aryl refers to a monocyclic or polycyclic hydrocarbon residue in which at least one carbocyclic ring is present that has a conjugated pi electron system. In a (C_6-C_{14})-aryl residue from 6 to 14 ring carbon atoms are present. Examples of (C_6-C_{14})-aryl residues are phenyl, naphthyl, biphenylyl, fluorenyl or anthracenyl. Unless stated otherwise, and irrespective of any specific substituents bonded to aryl groups which are indicated in the definition of the compounds of the formula I, aryl residues, for example phenyl, naphthyl or fluorenyl, can in general be unsubstituted or substituted by one or more, for example one, two or three, identical or different substituents. Aryl residues can be bonded via any desired position, and in substituted aryl residues the substituents can be located in any desired position.

[0027] Unless stated otherwise, and irrespective of any specific substituents bonded to aryl groups which are indicated in the definition of the compounds of the formula I, substituents that can be present in substituted aryl groups are, for example, (C_1-C_8)-alkyl, in particular (C_1-C_4)-alkyl, such as methyl, ethyl or tBu, hydroxy, (C_1-C_8)-alkyloxy, in particular (C_1-C_4)-alkyloxy, such as methoxy, ethoxy or tert-butoxy, methylenedioxy, ethylenedioxy, F, Cl, Br, I, cyano, nitro, trifluoromethyl, trifluoromethoxy, hydroxymethyl, formyl, acetyl, amino, mono- or di-(C_1-C_4)-alkylamino, ((C_1-C_4)-alkyl)carbonylamino like acetylamino, hydroxycarbonyl, ((C_1-C_4)-alkyloxy)carbonyl, carbamoyl, benzyl optionally substituted in the phenyl group, optionally substituted phenyl, optionally substituted phenoxy or benzyloxy optionally substituted in the phenyl group. A substituted aryl group which is present in a specific position of the compounds of formula I can independently of other aryl groups be substituted by substituents selected from any desired subgroup of the substituents listed before and/or in the specific definition of that group. For example, a substituted aryl group may be substituted by one or more identical or different substituents chosen from (C_1-C_4)-alkyl, hydroxy, (C_1-C_4)-alkyloxy, F, Cl, Br, I, cyano, nitro, trifluoromethyl, amino, phenyl, benzyl, phenoxy and benzyloxy. In general, preferably not more than two nitro groups are present in the compounds of the formula I.

[0028] In monosubstituted phenyl residues the substituent can be located in the 2-position, the 3-position or the 4-position, with the 3-position and the 4-position being preferred. If a phenyl group carries two substituents, they can be located in 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In phenyl residues carrying three substituents the substituents can be located in 2,3,4-position, 2,3,5-position, 2,3,6-position, 2,4,5-position, 2,4,6-position, or 3,4,5-position. Naphthyl residues can be 1-naphthyl and 2-naphthyl. In substituted naphthyl residues

the substituents can be located in any positions, for example in monosubstituted 1-naphthyl residues in the 2-, 3-, 4-, 5-, 6-, 7-, or 8-position and in monosubstituted 2-naphthyl residues in the 1-, 3-, 4-, 5-, 6-, 7-, or 8-position. Biphenylyl residues can be 2-biphenylyl, 3-biphenylyl and 4-biphenylyl. Fluorenyl residues can be 1-, 2-, 3-, 4- or 9-fluorenyl. In monosubstituted fluorenyl residues bonded via the 9-position the substituent is preferably present in the 1-, 2-, 3- or 4-position.

[0029] A 4-15 membered mono- or polycyclic group, which can contain, zero, one, two, three or four heteroatoms, such as nitrogen, sulfur or oxygen comprises groups containing 4 to 15 ring atoms in the parent monocyclic or bicyclic carbocyclic or heterocyclic ring system. In monocyclic groups the carbocyclic or heterocyclic ring preferably is a 5-membered, 6-membered or 7-membered ring, particularly preferably a 5-membered or 6-membered ring. In bicyclic groups preferably two fused rings are present one of which is a 5-membered ring or 6-membered carbocyclic or heterocyclic ring and the other of which is a 5-membered or 6-membered heterocyclic or carbocyclic ring, i. e. a bicyclic ring preferably contains 8, 9 or 10 ring atoms, particularly preferably 9 or 10 ring atoms. It comprises saturated carbocyclic or heterocyclic ring systems which do not contain any double bonds within the rings, as well as mono-unsaturated and poly-unsaturated carbocyclic or heterocyclic ring systems which contain one or more, for example one, two, three, four or five, double bonds within the rings provided that the resulting system is stable. Unsaturated rings may be non-aromatic or aromatic, i. e. double bonds within the rings in this group may be arranged in such a manner that a conjugated pi electron system results. Aromatic rings in a group may be 5-membered or 6-membered rings, i. e. aromatic groups in a group contain 5 to 10 ring atoms. Aromatic rings in this group thus comprise 5-membered and 6-membered monocyclic carbocycles or heterocycles and bicyclic carbocycles or heterocycles composed of two 5-membered rings, one 5-membered ring and one 6-membered ring, or two 6-membered rings. In bicyclic aromatic groups one or both rings may contain heteroatoms. Aromatic groups may also be referred to by the customary term aryl or heteroaryl for which all the definitions and explanations above and below correspondingly apply.

Examples for carbocyclic groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl, decahydronaphthaline, twistan (= tricyclo[4.4.0.0^{3,8}]decan), adamantane (= tricyclo[3.3.1.1^{3,7}]decan), noradamantane (= tricyclo[3.3.1.0^{3,7}]nonane), tricyclo[2.2.1.0^{2,6}]heptane, tricyclo[5.3.2.0^{4,9}]dodecane, tricyclo[5.4.0.0^{2,9}]undecaneor tricyclo[5.5.1.0^{3,11}]tridecane.

In heterocyclic groups preferably 1, 2, 3 or 4 identical or different ring heteroatoms chosen from nitrogen, oxygen and sulfur are present. Particularly preferably in these groups one or two identical or different heteroatoms chosen from nitrogen, oxygen and sulfur are present. The ring heteroatoms can be present in any desired number and in any position with respect to each other provided that the resulting heterocyclic system is known in the art and is stable and suitable as a subgroup in a drug substance. Examples of parent structures of heterocycles from which the 4-15 membered mono- or polycyclic group can be derived are aziridine, oxirane, azetidine, pyrrole, furan, thiophene, dioxole, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyran, thiopyran, pyridazine, pyrimidine, pyrazine, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, azepine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, indole, isoindole, benzofuran, benzothiophene, 1,3-benzodioxole, indazole, benzimidazole, benzoxazole, benzothiazole, quinoline, isoquinoline, chromane, isochromane, cinnoline, quinazoline, quinoxaline, phthalazine, pyridoimidazoles, pyridopyridines, pyridopyrimidines, purine, pteridine etc. as well as ring systems which result from the listed heterocycles by fusion (or condensation) of a carbocyclic ring, for example benzo-fused, cyclopenta-fused, cyclohexa-fused or cyclohepta-fused derivatives of these heterocycles.

The fact that many of the before-listed names of heterocycles are the chemical names of unsaturated or aromatic ring systems does not imply that the , the 4-15 membered mono- or polycyclic group could only be derived from the respective unsaturated ring system. The names here only serve to describe the ring system with respect to ring size and the number of the heteroatoms and their relative positions. As explained above, the 4-15 membered mono- or polycyclic group can be saturated or partially unsaturated or aromatic, and can thus be derived not only from the before-listed heterocycles themselves but also from all their partially or completely hydrogenated analogues and also from their more highly unsaturated analogues if applicable. As examples of completely or partially hydrogenated analogues of the before-listed heterocycles from which this group may be derived the following may be mentioned: pyrroline, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, dihydropyridine, tetrahydropyridine, piperidine, 1,3-dioxolane, 2-imidazoline, imidazolidine, 4,5-dihydro-1,3-oxazol, 1,3-oxazolidine, 4,5-dihydro-1,3-thiazole, 1,3-thiazolidine, perhydro-1,4-dioxane, piperazine, perhydro-1,4-oxazine (= morpholine), perhydro-1,4-thiazine (= thiomorpholine), perhydroazepine, indoline, isoindoline, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, etc. The 4-15 membered mono- or polycyclic group may be bonded via any ring carbon atom, and in the case of nitrogen heterocycles via any suitable ring nitrogen atom. Thus, for example, a pyrrolyl residue can be 1-pyrrolyl, 2-pyrrolyl or 3-pyrrolyl, a pyrrolidinyl residue can be pyrrolidin-1-yl (= pyrrolidino), pyrrolidin-2-yl or pyrrolidin-3-yl, a pyridinyl residue can be pyridin-2-yl, pyridin-3-yl or pyridin-4-yl, a piperidinyl residue can be piperidin-1-yl (= piperidino), piperidin-2-yl, piperidin-3-yl or piperidin-4-yl. Furyl can be 2-furyl or 3-furyl, thienyl can be 2-thienyl or 3-thienyl, imidazolyl can be imidazol-1-yl, imidazol-2-yl, imidazol-4-yl or imidazol-5-yl, 1,3-oxazolyl can be 1,3-oxazol-2-yl, 1,3-oxazol-4-yl or 1,3-oxazol-5-yl, 1,3-thiazolyl

can be 1,3-thiazol-2-yl, 1,3-thiazol-4-yl or 1,3-thiazol-5-yl, pyrimidinyl can be pyrimidin-2-yl, pyrimidin-4-yl (= 6-pyrimidinyl) or 5-pyrimidinyl, piperazinyl can be piperazin-1-yl (= piperazin-4-yl = piperazino) or piperazin-2-yl. Indolyl can be indol-1-yl, indol-2-yl, indol-3-yl, indol-4-yl, indol-5-yl, indol-6-yl or indol-7-yl. Similarly benzimidazolyl, benzoxazolyl and benzothiazol residues can be bonded via the 2-position and via any of the positions 4, 5, 6, and 7. Quinolinyl can be quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl, quinolin-6-yl, quinolin-7-yl or quinolin-8-yl, isoqinolinyl can be isoquinol-1-yl, isoquinolin-3-yl, isoquinolin-4-yl, isoquinolin-5-yl, isoquinolin-6-yl, isoquinolin-7-yl or isoquinolin-8-yl. In addition to being bonded via any of the positions indicated for quinolinyl and isoquinolinyl, 1,2,3,4-tetrahydroquinolinyl and 1,2,3,4-tetrahydroisoquinolinyl can also be bonded via the nitrogen atoms in 1-position and 2-position, respectively. Unless stated otherwise, and irrespective of any specific substituents bonded to the 4-15 membered mono- or polycyclic group or any other heterocyclic groups which are indicated in the definition of the compounds of the formula I, the 4-15 membered mono- or polycyclic group can be unsubstituted or substituted on ring carbon atoms with one or more, for example one, two, three, four or five, identical or different substituents like (C_1-C_8)-alkyl, in particular (C_1-C_4)-alkyl, (C_1-C_8)-alkyloxy, in particular (C_1-C_4)-alkyloxy, (C_1-C_4)-alkylthio, halogen, nitro, amino, ((C_1-C_4)-alkyl)carbonylamino like acetylamino, trifluoromethyl, trifluoromethoxy, hydroxy, oxo, hydroxy-(C_1-C_4)-alkyl such as, for example, hydroxymethyl or 1-hydroxyethyl or 2-hydroxyethyl, methylenedioxy, ethylenedioxy, formyl, acetyl, cyano, aminosulfonyl, methylsulfonyl, hydroxycarbonyl, aminocarbonyl, (C_1-C_4)-alkyloxycarbonyl, optionally substituted phenyl, optionally substituted phenoxy, benzyl optionally substituted in the phenyl group, benzyloxy optionally substituted in the phenyl group, etc. The substituents can be present in any desired position provided that a stable molecule results. Of course an oxo group cannot be present in an aromatic ring. Each suitable ring nitrogen atom in the 4-15 membered mono- or polycyclic group can independently of each other be unsubstituted, i. e. carry a hydrogen atom, or can be substituted, i. e. carry a substituent like (C_1-C_8)-alkyl, for example (C_1-C_4)-alkyl such as methyl or ethyl, optionally substituted phenyl, phenyl-(C_1-C_4)-alkyl, for example benzyl, optionally substituted in the phenyl group, hydroxy-(C_2-C_4)-alkyl such as, for example 2-hydroxyethyl, acetyl or another acyl group, methylsulfonyl or another sulfonyl group, aminocarbonyl, (C_1-C_4)-alkyloxycarbonyl, etc. In general, in the compounds of the formula I nitrogen heterocycles can also be present as N-oxides or as quaternary salts. Ring sulfur atoms can be oxidized to the sulfoxide or to the sulfone. Thus, for example a tetrahydrothienyl residue may be present as S,S-dioxotetrahydrothienyl residue or a thiomorpholinyl residue like thiomorpholin-4-yl may be present as 1-oxo-thiomorpholin-4-yl or 1,1-dioxo-thiomorpholin-4-yl. A substituted 4-15 membered mono- or polycyclic group that can be present in a specific position of the compounds of formula I can independently of other groups be substituted by substituents selected from any desired subgroup of the substituents listed before and/or in the definition of that group.

[0030] Examples for a 5 to 7-membered monocyclic hetreocyclic ring, containing at least one nitrogen atom and which is optionally substituted by oxo are piperidine, morholine, piperazine, thiomorholine, pyrrolidine, pyrrolidinone, ketopiperazine.

[0031] A 3-7 membered monocyclic group, which can contain, zero, one, two, three or four heteroatoms, such as nitrogen, sulfur or oxygen comprises groups containing 3 to 7 ring atoms in the parent monocyclic carbocyclic or heterocyclic ring system. The carbocyclic or heterocyclic ring preferably is a 5-membered or a 6-membered ring.
It comprises saturated carbocyclic or heterocyclic ring systems which do not contain any double bonds within the rings, as well as mono-unsaturated and poly-unsaturated carbocyclic or heterocyclic ring systems which contain one or more, for example one, two or three double bonds within the ring, provided that the resulting system is stable.

[0032] Unsaturated rings may be non-aromatic or aromatic, i. e. double bonds within the rings in this group may be arranged in such a manner that a conjugated pi electron system results. Aromatic rings in this group thus comprise 5-membered and 6-membered monocyclic carbocycles or heterocycles. Aromatic groups may also be referred to by the customary term aryl or heteroaryl for which all the definitions and explanations above and below correspondingly apply.
Examples for carbocyclic groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.
In heterocyclic groups preferably 1, 2, 3 or 4 identical or different ring heteroatoms chosen from nitrogen, oxygen and sulfur are present. Particularly preferably in these groups one or two identical or different heteroatoms chosen from nitrogen, oxygen and sulfur are present. The ring heteroatoms can be present in any desired number and in any position with respect to each other provided that the resulting heterocyclic system is known in the art and is stable and suitable as a subgroup in a drug substance. Examples of parent structures of heterocycles from which the 3-7 membered monocyclic group can be derived are aziridine, oxirane, azetidine, pyrrole, furan, thiophene, dioxole, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyran, thiopyran, pyridazine, pyrimidine, pyrazine, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, azepine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine etc.

[0033] The fact that many of the before-listed names of heterocycles are the chemical names of unsaturated or aromatic ring systems does not imply that the , the 3-7 membered monocyclic group can only be derived from the respective unsaturated ring system. The names here only serve to describe the ring system with respect to ring size and the number of the heteroatoms and their relative positions. As explained above, the 3-7 membered monocyclic

group can be saturated or partially unsaturated or aromatic, and can thus be derived not only from the before-listed heterocycles themselves but also from all their partially or completely hydrogenated analogues and also from their more highly unsaturated analogues if applicable. As examples of completely or partially hydrogenated analogues of the before-listed heterocycles from which this group may be derived the following may be mentioned: pyrroline, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, dihydropyridine, tetrahydropyridine, piperidine, 1,3-dioxolane, 2-imidazoline, imidazolidine, 4,5-dihydro-1,3-oxazol, 1,3-oxazolidine, 4,5-dihydro-1,3-thiazole, 1,3-thiazolidine, perhydro-1,4-dioxane, piperazine, perhydro-1,4-oxazine (= morpholine), perhydro-1,4-thiazine (= thiomorpholine), perhydroazepine etc.

[0034] The 3-7 membered monocyclic group may be bonded via any ring carbon atom, and in the case of nitrogen heterocycles via any suitable ring nitrogen atom. Thus, for example, a pyrrolyl residue can be 1-pyrrolyl, 2-pyrrolyl or 3-pyrrolyl, a pyrrolidinyl residue can be pyrrolidin-1-yl (= pyrrolidino), pyrrolidin-2-yl or pyrrolidin-3-yl, a pyridinyl residue can be pyridin-2-yl, pyridin-3-yl or pyridin-4-yl, a piperidinyl residue can be piperidin-1-yl (= piperidino), piperidin-2-yl, piperidin-3-yl or piperidin-4-yl. Furyl can be 2-furyl or 3-furyl, thienyl can be 2-thienyl or 3-thienyl, imidazolyl can be imidazol-1-yl, imidazol-2-yl, imidazol-4-yl or imidazol-5-yl, 1,3-oxazolyl can be 1,3-oxazol-2-yl, 1,3-oxazol-4-yl or 1,3-oxazol-5-yl, 1,3-thiazolyl can be 1,3-thiazol-2-yl, 1,3-thiazol-4-yl or 1,3-thiazol-5-yl, pyrimidinyl can be pyrimidin-2-yl, pyrimidin-4-yl (= 6-pyrimidinyl) or 5-pyrimidinyl, piperazinyl can be piperazin-1-yl (= piperazin-4-yl = piperazino) or piperazin-2-yl. Unless stated otherwise, and irrespective of any specific substituents bonded to the 3-7 membered monocyclic group or any other heterocyclic groups which are indicated in the definition of the compounds of the formula I, can be unsubstituted or substituted on ring carbon atoms with one or more, for example one, two, three, four or five, identical or different substituents like (C_1-C_8)-alkyl, in particular (C_1-C_4)-alkyl, (C_1-C_8)-alkyloxy, in particular (C_1-C_4)-alkyloxy, (C_1-C_4)-alkylthio, halogen, nitro, amino, ((C_1-C_4)-alkyl)carbonylamino like acetylamino, trifluoromethyl, trifluoromethoxy, hydroxy, oxo, hydroxy-(C_1-C_4)-alkyl such as, for example, hydroxymethyl or 1-hydroxyethyl or 2-hydroxyethyl, methylenedioxy, ethylenedioxy, formyl, acetyl, cyano, aminosulfonyl, methylsulfonyl, hydroxycarbonyl, aminocarbonyl, (C_1-C_4)-alkyloxycarbonyl, optionally substituted phenyl, optionally substituted phenoxy, benzyl optionally substituted in the phenyl group, benzyloxy optionally substituted in the phenyl group, etc. The substituents can be present in any desired position provided that a stable molecule results. Of course an oxo group cannot be present in an aromatic ring. Each suitable ring nitrogen atom in the 3-7 membered monocyclic group can independently of each other be unsubstituted, i. e. carry a hydrogen atom, or can be substituted, i. e. carry a substituent like (C_1-C_8)-alkyl, for example (C_1-C_4)-alkyl such as methyl or ethyl, optionally substituted phenyl, phenyl-(C_1-C_4)-alkyl, for example benzyl, optionally substituted in the phenyl group, hydroxy-(C_2-C_4)-alkyl such as, for example 2-hydroxyethyl, acetyl or another acyl group, methylsulfonyl or another sulfonyl group, aminocarbonyl, (C_1-C_4)-alkyloxycarbonyl, etc. In general, in the compounds of the formula I nitrogen heterocycles can also be present as N-oxides or as quaternary salts. Ring sulfur atoms can be oxidized to the sulfoxide or to the sulfone. Thus, for example a tetrahydrothienyl residue may be present as S, S-dioxotetrahydrothienyl residue or a thiomorpholinyl residue like thiomorpholin-4-yl may be present as 1-oxo-thiomorpholin-4-yl or 1,1-dioxo-thiomorpholin-4-yl. A substituted 3-7 membered monocyclic group that can be present in a specific position of the compounds of formula I can independently of other groups be substituted by substituents selected from any desired subgroup of the substituents listed before and/or in the definition of that group.

[0035] Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine, particularly preferably chlorine or bromine.

[0036] Optically active carbon atoms present in the compounds of the formula I can independently of each other have R configuration or S configuration. The compounds of the formula I can be present in the form of pure enantiomers or pure diastereomers or in the form of mixtures of enantiomers and/or diastereomers, for example in the form of racemates. The present invention relates to pure enantiomers and mixtures of enantiomers as well as to pure diastereomers and mixtures of diastereomers. The invention comprises mixtures of two or of more than two stereoisomers of the formula I, and it comprises all ratios of the stereoisomers in the mixtures. In case the compounds of the formula I can be present as E isomers or Z isomers (or cis isomers or trans isomers) the invention relates both to pure E isomers-and pure Z isomers and to E/Z mixtures in all ratios. The invention also comprises all tautomeric forms of the compounds of the formula I.

[0037] Diastereomers, including E/Z isomers, can be separated into the individual isomers, for example, by chromatography. Racemates can be separated into the two enantiomers by customary methods, for example by chromatography on chiral phases or by resolution, for example by crystallization of diastereomeric salts obtained with optically active acids or bases. Stereochemically unifom compounds of the formula I can also be obtained by employing stereochemically uniform starting materials or by using stereoselective reactions.

[0038] The choice of incorporating into a compound of the formula I a building block with R configuration or S configuration, or in the case of an amino acid unit present in a compound of the formula I of incorporating a building block designated as D-amino acid or L-amino acid, can depend, for example, on the desired characteristics of the compound of the formula I. For example, the incorporation of a D-amino acid building block can confer increased stability in vitro or in vivo. The incorporation of a D-amino acid building block also can achieve a desired increase or decrease in the

pharmacological activity of the compound. In some cases it can be desirable to allow the compound to remain active for only a short period of time. In such cases, the incorporation of an L-amino acid building block in the compound can allow endogenous peptidases in an individual to digest the compound in vivo, thereby limiting the individual's exposure to the active compound. A similar effect may also be observed in the compounds of the invention by changing the configuration in another building block from S configuration to R configuration or vice versa. By taking into consideration the medical needs one skilled in the art can determine the desirable characteristics, for example a favorable stereochemistry, of the required compound of the invention.

[0039] Physiologically tolerable salts of the compounds of formula I are nontoxic salts that are physiologically acceptable, in particular pharmaceutically utilizable salts. Such salts of compounds of the formula I containing acidic groups, for example a carboxy group COOH, are for example alkali metal salts or alkaline earth metal salts such as sodium salts, potassium salts, magnesium salts and calcium salts, and also salts with physiologically tolerable quaternary ammonium ions such as tetramethylammonium or tetraethylammonium, and acid addition salts with ammonia and physiologically tolerable organic amines, such as methylamine, dimethylamine, trimethylamine, ethylamine, triethylamine, ethanolamine or tris-(2-hydroxyethyl)amine. Basic groups contained in the compounds of the formula I, for example amino groups or guanidino groups, form acid addition salts, for example with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid or phosphoric acid, or with organic carboxylic acids and sulfonic acids such as formic acid, acetic acid, oxalic acid, citric acid, lactic acid, malic acid, succinic acid, malonic acid, benzoic acid, maleic acid, fumaric acid, tartaric acid, methanesulfonic acid or p-toluenesulfonic acid. Compounds of the formula I which simultaneously contain a basic group and an acidic group, for example a guanidino group and a carboxy group, can also be present as zwitterions (betaines) which are likewise included in the present invention.

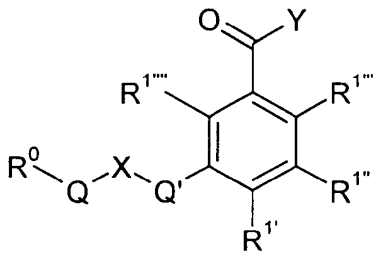
[0040] Salts of compounds of the formula I can be obtained by customary methods known to those skilled in the art, for example by combining a compound of the formula I with an inorganic or organic acid or base in a solvent or dispersant, or from other salts by cation exchange or anion exchange. The present invention also includes all salts of the compounds of the formula I which, because of low physiologically tolerability, are not directly suitable for use in pharmaceuticals but are suitable, for example, as intermediates for carrying out further chemical modifications of the compounds of the formula I or as starting materials for the preparation of physiologically tolerable salts. The present invention furthermore includes all solvates of compounds of the formula I, for example hydrates or adducts with alcohols.

[0041] The invention also includes derivatives and modifications of the compounds of the formula I, for example prodrugs, protected forms and other physiologically tolerable derivatives, as well as active metabolites of the compounds of the formula I. The invention relates in particular to prodrugs and protected forms of the compounds of the formula I which can be converted into compounds of the formula I under physiological conditions. Suitable prodrugs for the compounds of the formula I, i. e. chemically modified derivatives of the compounds of the formula I having properties which are improved in a desired manner, for example with respect to solubility, bioavailability or duration of action, are known to those skilled in the art. More detailed information relating to prodrugs is found in standard literature like, for example, Design of Prodrugs, H. Bundgaard (ed.), Elsevier, 1985,, Fleisher et al., Advanced Drug Delivery Reviews 19 (1996) 115-130; or H. Bundgaard, Drugs of the Future 16 (1991) 443 which are all incorporated herein by reference. Suitable prodrugs for the compounds of the formula I are especially acyl prodrugs and carbamate prodrugs of acylatable nitrogen-containing groups such as amino groups and the guanidino group and also ester prodrugs and amide prodrugs of carboxylic acid groups which may be present in compounds of the formula I. In the acyl prodrugs and carbamate prodrugs one or more, for example one or two, hydrogen atoms on nitrogen atoms in such groups are replaced with an acyl group or a carbamate, preferably a (C_1-C_6)-alkyloxycarbonyl group. Suitable acyl groups and carbamate groups for acyl prodrugs and carbamate prodrugs are, for example, the groups R^{p1}-CO- and R^{p2}O-CO-, in which R^{p1} is hydrogen, (C_1-C_{18})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_4)-alkyl-, (C_6-C_{14})-aryl, Het-, (C_6-C_{14})-aryl-(C_1-C_4)-alkyl- or Het-(C_1-C_4)-alkyl- and in which R^{p2} has the meanings indicated for R^{p1} with the exception of hydrogen.

[0042] X) The present invention also relates to processes of preparation by which the compounds of the formula I are obtainable and which comprise carrying out one or more of the synthesis steps described below. The compounds of the formula I can generally be prepared using procedures described below, together with synthetic methods known to those skilled in the art of organic synthesis (see e.g. J. March, Advanced Organic Chemistry, Fourth Edition, John Wiley & Sons, 1992),, or variations thereon as appreciated by those skilled in the art, for example in the course of a convergent synthesis, by linkage of two or more fragments which can be derived retrosynthetically from the formula I and the synthesis of those fragments is known to those skilled in the art. In the course of the preparation of the compounds of the formula I it can generally be advantageous or necessary to introduce functional groups which could lead to undesired reactions or side reactions in the respective synthesis step, in the form of precursor groups which are later converted into the desired functional groups, or to temporarily block functional groups by a protective group strategy suited to the synthesis problem. Such strategies are well known to those skilled in the art (see, for example, Greene and Wuts, Protective Groups in Organic Synthesis, Wiley, 1991). As examples of precursor groups nitro groups and cyano groups may be mentioned which can later be converted by reduction, for example by catalytic hydrogenation,

into amino groups and aminomethyl groups, respectively. Protective groups can also have the meaning of a solid phase, and cleavage from the solid phase stands for the removal of the protective group. The use of such techniques is known to those skilled in the art (Burgess K (Ed.) Solid Phase Organic Synthesis ,New York: Wiley, 2000). For example, a phenolic hydroxy group can be attached to a trityl-polystyrene resin, which serves as a protecting group, and the molecule is cleaved from this resin by treatment with TFA at a later stage of the synthesis.

[0043] For example, for the preparation of one of the compounds of the formula I, in which W is phenyl, and in which U has the meaning of $-(CH_2)_0C(O)NR^{10}(CH_2)_1-$, a building block of the formula XI,



XI

in which R^0, Q, Q', X, are as defined above for the compounds of the formula I but functional groups of the formula XI can optionally also be present in the form of precursor groups or can be protected by protective groups known to those skilled in the art, e.g. an amino group can be protected with a tert.-butyloxycarbonyl group or a benzyloxycarbonyl group. $R^{1'}$, $R^{1''}$, $R^{1'''}$, $R^{1''''}$, are defined as hydrogen or as R^1 which has the same meaning as in formula I but can optionally also be present in the form of precursor groups or can be protected by protective groups known to those skilled in the art, e.g. a hydroxy group may be attached to a polystyrene resin, and Y is a nucleophilically substituable leaving group or a hydroxyl group, which may also be attached to a polystyrene resin, is reacted with a fragment of the formula XII

$$\mathbf{H\text{-}NR^{10}\text{-}V\text{-}G\text{-}M} \qquad \text{(XII)}$$

in which R^{10},V, G, and M are as defined above for the compounds of the formula I but functional groups of the formula XII can optionally also be present in the form of precursor groups or can be protected by protective groups.

[0044] The group COY in the formula XI is preferably the carboxylic acid group COOH or an activated carboxylic acid derivative. Y can thus be, for example, hydroxyl, halogen, in particular chlorine or bromine, alkoxy, in particular methoxy or ethoxy, aryloxy, for example phenoxy or pentafluorophenoxy, phenylthio, methylthio, 2-pyridylthio or a residue of a nitrogen heterocycle bonded via a nitrogen atom, in particular a residue of an azole, such as, for example, 1-imidazolyl. Y can furthermore be, for example, $((C_1\text{-}C_4)$-alkyl)-O-CO-O- or tolylsulfonyloxy and the activated acid derivative can thus be a mixed anhydride.

[0045] If Y is hydroxyl, then the carboxylic acid is expediently first activated, for example by one of the various methods used for peptide couplings which are well known to those skilled in the art. Examples of suitable activation agents are O-((cyano(ethoxycarbonyl) methylene)amino)-1,1,3,3-tetramethyluronium tetrafluoroborate (TOTU) ; (König et al., Proc. 21st Europ. Peptide Symp. 1990 (eds. Giralt, Andreu), Escom, Leiden 1991, p. 143), O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) (L. A. Carpino, J. Am. Chem. Soc. 1993, 115, 4397), or carbodiimides like dicyclohexylcarbodiimide or diisopropylcarbodiimide. The activation of the carboxylic acid function may also favorably be carried, for example, by conversion of the carboxylic acid group into the pentafluorophenyl ester using dicyclohexylcarbodiimide and pentafluorophenol. A number of suitable methods for the preparation of activated carboxylic acid derivatives are also indicated with details of source literature in J. March, Advanced Organic Chemistry, Fourth Edition, John Wiley & Sons, 1992. The activation and the subsequent reaction with the compound of the formula III are usually carried in the presence of an inert solvent or diluent, for example DCM, chloroform, THF, diethyl ether, n-heptane, n-hexane, n-pentane, cyclohexane, diisopropyl ether, methyl tBu ether, acetonitrile, DMF, DMSO, dioxane, toluene, benzene, ethyl acetate or a mixture of these solvents, if appropriate with addition of a base such as, for example, potassium tert-butoxide or tributylamine or triethylamine or diisopropylethylamine.

[0046] The resulting product is a compound of the formula I in which functional groups can also be present in the form of precursor groups or can be protected by protective groups. If still any protective groups or precursor groups are present they are then removed by known methods (see Greene and Wuts, Protective Groups in Organic Synthesis,

Wiley, 1991), or converted in the desired final groups, respectively. E.g. , if a carboxylic acid group protected as tBu ester and the free carboxylic acid is to be prepared as the final compound the protective group can be removed by reaction with trifluoroacetic acid or tert.-butyloxycarbonyl protecting groups can be removed by treatment with trifluoroacetic acid. If desired, with the obtained compounds further reactions can then be carried out by standard processes, for example acylation reactions or esterification reactions, or the compounds can be converted into physiologically tolerable salts or prodrugs by standard processes known to those skilled in the art.

[0047] Other compounds of the formula I can be prepared in a similar fashion as described above by coupling of a compound of the formula XIII with a compound of the formula XII.

$$R^0\text{-}Q\text{-}X\text{-}Q'\text{-}W\text{-}C(O)\text{-}Y \qquad (XII)$$

in which R^0, Q, Q', X, W and Y are as defined above for the compounds of the formula I but functional groups can optionally also be present in the form of precursor groups or can be protected by protective groups known to those skilled in the art, e.g. an amino group can be protected with a tert.-butyloxycarbonyl group or a benzyloxycarbonyl group or a hydroxy group may be attached to a polystyrene resin.

[0048] The compounds of the formula XI, XII and XIII are prepared by methods well known to those skilled in the art (E.g. in J March, Advanced Organic Chemistry, 4th Edition, John Wiley & Sons, 1992; RC Larock, Comprehensive Organic Transformations, VCH Publishers, New York 1989).

[0049] Preferred methods include, but are not limited to those described in the examples.

[0050] The compounds of the present invention are serine protease inhibitors which inhibit the activity of the blood coagulation enzymes factor Xa and/or factor VIIa. In particular, they are highly active inhibitors of factor Xa. They are specific serine protease inhibitors inasmuch as they do not substantially inhibit the activity of other proteases whose inhibition is not desired. The activity of the compounds of the formula I can be determined, for example, in the assays described below or in other assays known to those skilled in the art. With respect to factor Xa inhibition, a preferred embodiment of the invention comprises compounds which have a Ki $\leq$ 1 for factor Xa inhibition as determined in the assay described below, with or without concomitant factor VIIa inhibition, and which preferably do not substantially inhibit the activity of other proteases involved in coagulation and fibrinolysis whose inhibition is not desired (using the same concentration of the inhibitor). The compounds of the invention inhibit factor Xa catalytic activity either directly, within the prothrombinase complex or as a soluble subunit, or indirectly, by inhibiting the assembly of factor Xa into the prothrombinase complex.

[0051] XI) The present invention also relates to the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for use as pharmaceuticals (or medicaments), to the use of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for the production of pharmaceuticals for inhibition of factor Xa and/or factor VIIa or for influencing blood coagulation, inflammatory response or fibrinolysis or for the therapy or prophylaxis of the diseases mentioned above or below, for example for the production of pharmaceuticals for the therapy and prophylaxis of cardiovascular disorders, thromboembolic diseases or restenoses. The invention also relates to the use of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for the inhibition of factor Xa and/or factor VIIa or for influencing blood coagulation or fibrinolysis or for the therapy or prophylaxis of the diseases mentioned above or below, for example for use in the therapy and prophylaxis of cardiovascular disorders, thromboembolic diseases or restenoses, and to methods of treatment aiming at such purposes including methods for said therapies and prophylaxis. The present invention also relates to pharmaceutical preparations (or pharmaceutical compositions) which contain an effective amount of at least one compound of the formula I and/or its physiologically tolerable salts and/or its prodrugs in addition to a customary pharmaceutically acceptable carrier, i. e. one or more pharmaceutically acceptable carrier substances or excipients and/or auxiliary substances or additives.

[0052] XII) Preferred are the treatment of disease states such as abnormal thrombus formation, acute myocardial infarction, unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy or percutaneous transluminal coronary angioplasty, transient ischemic attacks, stroke, pathologic thrombus formation occuring in the veins of the lower extremities following abdominal, knee and hip surgery, a risk of pulmonary thromboembolism, or disseminated systemic intravascular coagulatopathy ocurring in vascular systems during septic shock, certain viral infections or cancer.

[0053] The compounds of the formula I and their physiologically tolerable salts and their prodrugs can be administered to animals, preferably to mammals, and in particular to humans as pharmaceuticals for therapy or prophylaxis. They can be administered on their own, or in mixtures with one another or in the form of pharmaceutical preparations which permit enteral or parenteral administration.

[0054] The pharmaceuticals can be administered orally, for example in the form of pills, tablets, lacquered tablets, coated tablets, granules, hard and soft gelatin capsules, solutions, syrups, emulsions, suspensions or aerosol mixtures.

Administration, however, can also be carried out rectally, for example in the form of suppositories, or parenterally, for example intravenously, intramuscularly or subcutaneously, in the form of injection solutions or infusion solutions, microcapsules, implants or rods, or percutaneously or topically, for example in the form of ointments, solutions or tinctures, or in other ways, for example in the form of aerosols or nasal sprays.

The pharmaceutical preparations according to the invention are prepared in a manner known per se and familiar to one skilled in the art, pharmaceutically acceptable inert inorganic and/or organic carriers being used in addition to the compound(s) of the formula I and/or its (their) physiologically tolerable salts and/or its (their) prodrugs. For the production of pills, tablets, coated tablets and hard gelatin capsules it is possible to use, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts, etc. Carriers for soft gelatin capsules and suppositories are, for example, fats, waxes, semisolid and liquid polyols, natural or hardened oils, etc. Suitable carriers for the production of solutions, for example injection solutions, or of emulsions or syrups are, for example, water, saline, alcohols, glycerol, polyols, sucrose, invert sugar, glucose, vegetable oils, etc. Suitable carriers for microcapsules, implants or rods are, for example, copolymers of glycolic acid and lactic acid. The pharmaceutical preparations normally contain about 0.5 % to 90 % by weight of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs. The amount of the active ingredient of the formula I and/or its physiologically tolerable salts and/or its prodrugs in the pharmaceutical preparations normally is from about 0.5 mg to about 1000 mg, preferably from about 1 mg to about 500 mg.

[0055] In addition to the active ingredients of the formula I and/or their physiologically acceptable salts and/or prodrugs and to carrier substances, the pharmaceutical preparations can contain additives such as, for example, fillers, disintegrants, binders, lubricants, wetting agents, stabilizers, emulsifiers, preservatives, sweeteners, colorants, flavorings, aromatizers, thickeners, diluents, buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants. They can also contain two or more compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs. In case a pharmaceutical preparation contains two or more compounds of the formula I the selection of the individual compounds can aim at a specific overall pharmacological profile of the pharmaceutical preparation. For example, a highly potent compound with a shorter duration of action may be combined with a long-acting compound of lower potency. The flexibility permitted with respect to the choice of substituents in the compounds of the formula I allows a great deal of control over the biological and physicochemical properties of the compounds and thus allows the selection of such desired compounds. Furthermore, in addition to at least one compound of the formula I and/or its physiologically tolerable salts and/or its prodrugs, the pharmaceutical preparations can also contain one or more other therapeutically or prophylactically active ingredients.

[0056] As inhibitors of factor Xa and/or factor VIIa the compounds of the formula I and their physiologically tolerable salts and their prodrugs are generally suitable for the therapy and prophylaxis of conditions in which the activity of factor Xa and/or factor VIIa plays a role or has an undesired extent, or which can favorably be influenced by inhibiting factor Xa and/or factor VIIa or decreasing their activities, or for the prevention, alleviation or cure of which an inhibition of factor Xa and/or factor VIIa or a decrease in their activity is desired by the physician. As inhibition of factor Xa and/or factor VIIa influences blood coagulation and fibrinolysis, the compounds of the formula I and their physiologically tolerable salts and their prodrugs are generally suitable for reducing blood clotting, or for the therapy and prophylaxis of conditions in which the activity of the blood coagulation system plays a role or has an undesired extent, or which can favorably be influenced by reducing blood clotting, or for the prevention, alleviation or cure of which a decreased activity of the blood coagulation system is desired by the physician. A specific subject of the present invention thus are the reduction or inhibition of unwanted blood clotting, in particular in an individual, by administering an effective amount of a compound I or a physiologically tolerable salt or a prodrug thereof, as well as pharmaceutical preparations therefor.

[0057] Conditions in which a compound of the formula I can be favorably used include, for example, cardiovascular disorders, thromboembolic diseases or complications associated, for example, with infection or surgery. The compounds of the present invention can also be used to reduce an inflammatory response. Examples of specific disorders for the treatment or prophylaxis of which the compounds of the formula I can be used are coronary heart disease, myocardial infarction, angina pectoris, vascular restenosis, for example restenosis following angioplasty like PTCA, adult respiratory disstress syndrome, multi-organ failure, stroke and disseminated intravascular clotting disorder. Examples of related complications associated with surgery are thromboses like deep vein and proximal vein thrombosis which can occur following surgery. In view of their pharmacological activity the compounds of the invention can replace or supplement other anticoagulant agents such as heparin. The use of a compound of the invention can result, for example, in a cost saving as compared to other anticoagulants.

When using the compounds of the formula I the dose can vary within wide limits and, as is customary and is known to the physician, is to be suited to the individual conditions in each individual case. It depends, for example, on the specific compound employed, on the nature and severity of the disease to be treated, on the mode and the schedule of administration, or on whether an acute or chronic condition is treated or whether prophylaxis is carried out. An appropriate dosage can be established using clinical approaches well known in the medical art. In general, the daily dose for achieving the desired results in an adult weighing about 75 kg is from 0.01 mg/kg to 100 mg/kg, preferably from 0.1

mg/kg to 50 mg/kg, in particular from 0.1 mg/kg to 10 mg/kg, (in each case in mg per kg of body weight). The daily dose can be divided, in particular in the case of the administration of relatively large amounts, into several, for example 2, 3 or 4, part administrations. As usual, depending on individual behavior it may be necessary to deviate upwards or downwards from the daily dose indicated.

[0058] A compound of the formula I can also advantageously be used as an anticoagulant outside an individual. For example, an effective amount of a compound of the invention can be contacted with a freshly drawn blood sample to prevent coagulation of the blood sample. Further, a compound of the formula I and its salts can be used for diagnostic purposes, for example in in vitro diagnoses, and as an auxiliary in biochemical investigations. For example, a compound of the formula I can be used in an assay to identify the presence of factor Xa and/or factor VIIa or to isolate factor Xa and/or factor VIIa in a substantially purified form. A compound of the invention can be labeled with, for example, a radioisotope, and the labeled compound bound to factor Xa and/or factor VIIa is then detected using a routine method useful for detecting the particular label. Thus, a compound of the formula I or a salt thereof can be used as a probe to detect the location or amount of factor Xa and/or factor VIIa activity in vivo, in vitro or ex vivo.

[0059] Furthermore, the compounds of the formula I can be used as synthesis intermediates for the preparation of other compounds, in particular of other pharmaceutical active ingredients, which are obtainable from the compounds of the formula I, for example by introduction of substituents or modification of functional groups.

[0060] The general synthetic sequences for preparing the compounds useful in the present invention our outlined in the examples given below. Both an explanation of, and the actual procedure for, the various aspects of the present invention are described where appropriate. The following examples are intended to be merely illustrative of the present invention, and not limiting thereof in either scope or spirit. Those with skill in the art will readily understand that known variations of the conditions and processes described in the examples can be used to synthesize the compounds of the present invention.

[0061] It is understood that changes that do not substantially affect the activity of the various embodiments of this invention are included within the invention disclosed herein. Thus, the following examples are intended to illustrate but not limit the present invention.

Examples

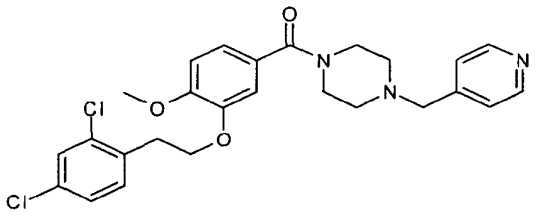
[0062] Abbreviations used:

tert-Butyl	tBu
2,2'-bis(diphenylphoshino-1,1'-binaphthyl	Binap
Bis-(oxo-3-oxazolidinyl)-phosphoryl chloride	BOP-Cl
dibenzylidenacetone	dba
Dichloromethane	DCM
Diethyl azodicarboxylate	DEAD
4-Dimethyaminopyridine	DMAP
N,N-Dimethylformamide	DMF
Dimethylsulfoxide	DMSO
O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate	HATU
N-Ethylmorpholine	NEM
Methanol	MeOH
Tetrahydrofuran	THF
Trifluoroacetic acid	TFA
O-((Ethoxycarbonyl)cyanomethyleneamino)-N,N,N',N'-tetramethyluronium tetrafluoroborate	TOTU

[0063] When in the final step of the synthesis of a compound an acid such as trifluoroacetic acid or acetic acid was used, for example when trifluoroacetic acid was employed to remove a tBu group or when a compound was purified by chromatography using an eluent which contained such an acid, in some cases, depending on the work-up procedure, for example the details of a freeze-drying process, the compound was obtained partially or completely in the form of a salt of the acid used, for example in the form of the acetic acid salt or trifluoroacetic acid salt or hydrochloric acid salt.

Example 1: {3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methoxy-phenyl}-(4-pyridin-4-ylmethyl-piperazin-1- yl)-methanone

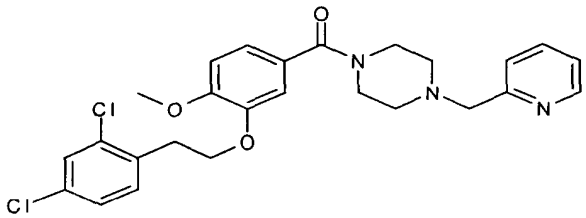
[0064]



0.100 g (0.29 mmol) of 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-benzoic acid was dissolved in 2 ml of DMF and treated with 0.146 ml (1.16 mmol) of N-NEM and 51 mg (0.29 mmol) of 1-Pyridin-4-ylmethyl-piperazine and 0.098 g (0.3 mmol) of TOTU. The solution was stirred for 1 h at RT. The solvent was removed under reduced pressure, the residue was taken-up in DCM and the solution was washed three times with saturated aqueous sodium bicarbonate. The organic phase was dried with sodium sulfate, filtered and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with n-heptane/ethyl acetate (1/1), ethyl acetate, and ethyl acetate/ MeOH (10/1). Yield 102 mg. MS (ES^+): m/e = 500 (M^+).

Example 2: {3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methoxy-phenyl}-(4-pyridin-2-ylmethyl-piperazin-1- yl)-methanone

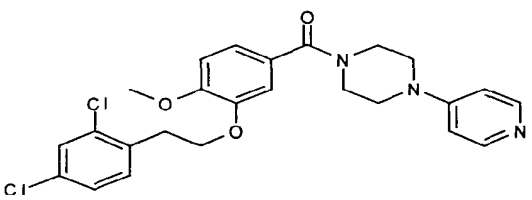
[0065]



0.100 g (0.29 mmol) of 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-benzoic acid was dissolved in 2 ml of DMF and treated with 0.146 ml (1.16 mmol) of N-NEM and 51 mg (0.29 mmol) of 1-Pyridin-2-ylmethyl-piperazine and 0.098 g (0.3 mmol) of TOTU. The solution was stirred for 1 h at RT. The solvent was removed under reduced pressure, the residue was taken-up in DCM and the solution was washed three times with saturated aqueous sodium bicarbonate. The organic phase was dried with sodium sulfate, filtered and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with n-heptane/ethyl acetate (1/1), ethyl acetate, and ethyl acetate/ MeOH (10/1). Yield 93 mg. MS (ES^+): m/e = 500 (M^+).

Example 3: {3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methoxy-phenyl}-(4-pyridin-4-yl-piperazin-1-yl)- methanone

[0066]

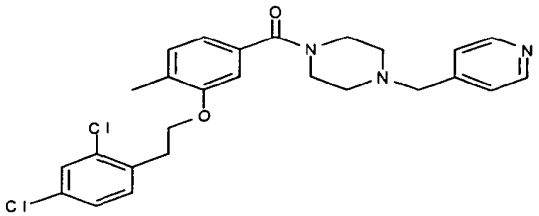


0.100 g (0.29 mmol) of 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-benzoic acid was dissolved in 2 ml of DMF and treated with 0.146 ml (1.16 mmol) of N-NEM and 47 mg (0.29 mmol) of 1-Pyridin-4-yl-piperazine and 0.098 g (0.3 mmol) of TOTU. The solution was stirred for 1 h at RT. The solvent was removed under reduced pressure, the residue was taken-up in DCM and the solution was washed three times with saturated aqueous sodium bicarbonate. The

organic phase was dried with sodium sulfate, filtered and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with n-heptane/ethyl acetate (1/1), ethyl acetate, and ethyl acetate/ MeOH (10/1). Yield 40 mg. MS (ES^+): m/e = 486 (M^+).

Example 4: {3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methyl-phenyl}-(4-pyridin-4-ylmethyl-piperazin-1- yl)-methanone

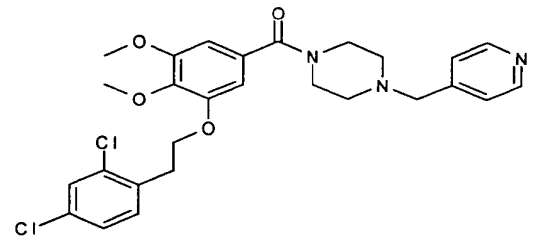
[0067]



0.094 g (0.29 mmol) of 3-[2-(2,4-dichioro-phenyi)-ethoxy]-4-methyi-benzoic acid was dissolved in 2 ml of DMF and treated with 0.146 ml (1.16 mmol) of N-NEM and 51 mg (0.29 mmol) of 1-Pyridin-4-ylmethyl-piperazine and 0.098 g (0.3 mmol) of TOTU. The solution was stirred for 16 h at RT. The solvent was removed under reduced pressure, the residue was taken-up in DCM and the solution was washed three times with saturated aqueous sodium bicarbonate. The organic phase was dried with sodium sulfate, filtered and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with DCM, and DCM/MeOH (20/1).
Yield 82 mg. MS (ES^+): m/e = 484 (M^+).

Example 5: {3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4,5-dimethoxy-phenyl}-(4-pyridin-4-ylmethyl-piperazin-1-yl)-methanone

[0068]



(i) 3-Hydroxy-4,5-dimethoxy-benzoic acid methyl ester

[0069] 5 g (27.2 mmol) of 3-Hydroxy-4,5-dimethoxy-benzoic acid was added at 0°C to 100 ml of a saturated solution of HCl in MeOH. The solution was stirred for 16 h at RT. The solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with ethyl acetate/n-heptane (2/1).
Yield 4.66g. MS (Cl^+): m/e = 212.2 (M^+).

(ii) 3-[2-(2,4-Dichlorophenyl)-ethoxy]-4,5-dimethoxy-benzoic acid

[0070] 2 g (9.42 mmol) of 3-Hydroxy-4,5-dimethoxy-benzoic acid methyl ester was dissolved in 100 ml of anhydrous tetrahydrofuran. To this solution was added 1.98g (10.37mmol) of 2-(2,4-Dichlorophenyl)-ethanol, 9.415 g (equivalent to 28.27 mmol PPh_3) of triphenylphosphine derivatized polystyrene and 4.924g (28.27 mmol) of DEAD. The solution was shaken for 16 h at RT. The polymer was filtered off and washed with ethyl acetate. The solvent was removed under reduced pressure. The residue was taken-up in ethyl acetate and the solution was washed three times with water and twice with saturated aqueous sodium chloride. The organic phase was dried with magnesium sulfate, filtered and the solvent was removed under reduced pressure.
The residue was dissolved in 20 ml of dioxan. 1 ml of water was added to the solution followed by 2N aqueous NaOH to give a pH of 13. The reaction solution was heated at 60 °C for 10 hours. The solution was cooled to 0 °C, 5 ml water

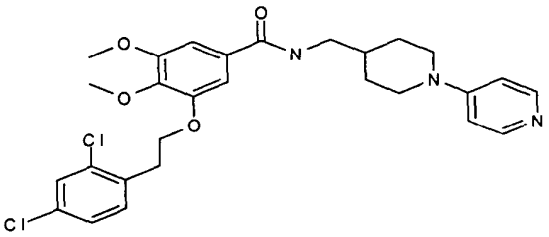
was added, followed by concentrated hydrochloric acid to give a pH of 1 to 2, whereupon the product precipitated from solution. The product was filtered off and dried under reduced pressure.
Yield 3.3g. MS (ES^-): m/e = 369 $(M-H)^-$.

(iii) {3-[2-(2,4-Dichlorophenyl)-ethoxy]-4,5-dimethoxy-phenyl}-(4-pyridin-4-ylmethyl-piperazin- 1-yl)-methanone

[0071] 0.100 g (0.269 mmol) of 3-[2-(2,4-Dichlorophenyl)-ethoxy]-4,5-dimethoxy-benzoic acid was dissolved in 2 ml of DMF and treated with 0.124 g (1.08 mmol) of N-NEM and 0.0477 g (0.27 mmol) of 1-Pyridin-4-ylmethyl-piperazine and 0.088 g (0.269 mmol) of TOTU. The solution was stirred for 16 h at RT. The solvent was removed under reduced pressure, the residue was taken-up in ethyl acetate and the solution was washed twice with saturated aqueous sodium bicarbonate and once with saturated aqueous sodium chloride. The organic phase was dried with magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with a gradient of 0-17% MeOH in DCM.
Yield 23.8 mg. MS (ES^+): m/e = 530 (M^+).

Example 6: 3-[2-(2,4-Dichlorophenyl)-ethoxy]-4,5-dimethoxy-N-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-benzamide

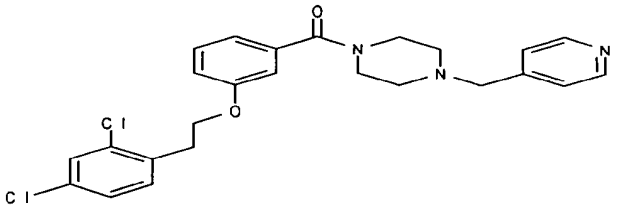
[0072]



0.100 g (0.269 mmol) of 3-[2-(2,4-Dichlorophenyl)-ethoxy]-4,5-dimethoxy-benzoic acid was dissolved in 2 ml of DMF and treated with 0.372 g (3.23 mmol) of N-NEM and 0.144 mg (0.27 mmol) of C-(3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-yl)-methylamine tris-trifluoroacetate salt and 0.088 g (0.269 mmol) of TOTU. The solution was stirred for 16 h at RT. The solvent was removed under reduced pressure, the residue was taken-up in ethyl acetate and the solution was washed twice with saturated aqueous sodium bicarbonate and once with saturated aqueous sodium chloride. The organic phase was dried with magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with a gradient of 0-17% MeOH in DCM. Yield 19.2 mg. MS (ES^+): m/e = 544 (M^+).

Example 7: {3-[2-(2,4-Dichloro-phenyl)-ethoxy]-phenyl)-(4-pyridin-4-ylmethyl-piperazin-1-yl)- methanone

[0073]



(i) 3-[2-(2,4-Dichlorophenyl)-ethoxy]-benzoic acid methyl ester

[0074] 2 g (13.1 mmol) of 3-hydroxybenzoic acid methyl ester and 4.75g (18.1 mmol) of triphenylphosphine were dissolved in 48 ml of anhydrous tetrahydrofuran. The solution was cooled to 0 °C and a solution of 3.04 g (17.5 mmol) DEAD in 7 ml of anhydrous tetrahydrofuran was added dropwise over 20 min. The solution was stirred at RT for 45

min. and a solution of 2.76g (14.5mmol) of 2-(2,4-Dichlorophenyl)-ethanol in 3ml anhydrous tetrahydrofuran was added. The reaction was stirred for 16 h at RT. The solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with ethyl acetate/n-heptane (4/1).
Yield 2.6 g. MS (Cl^+): m/e = 325 (M^+).

(ii) 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-benzoic acid

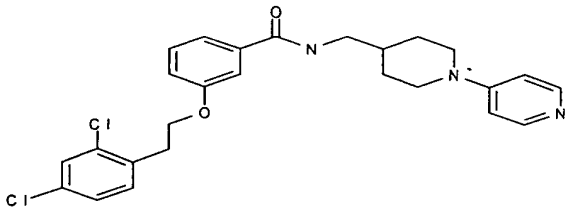
[0075] 1 g (3.07mmol) of 3-[2-(2,4-Dichlorophenyl)-ethoxy]-benzoic acid methyl ester was dissolved in 20 ml of dioxan. 2N aqueous NaOH was added to the solution to give a pH of 13. The reaction solution was heated at 50 °C for 3 h, and stirred at RT for 16h. 5 ml water was added, followed by concentrated hydrochloric acid to give a pH of 1 to 2, whereupon the product precipitated from solution. The suspension was stirred for 30min, then the product was filtered off and dried under reduced pressure.
Yield 0.92g. MS (Cl^+): m/e = 311 (M^+).

(iii) {3-[2-(2,4-Dichloro-phenyl)-ethoxy]-phenyl}-(4-pyridin-4-ylmethyl-piperazin-1-yl)-methanone

[0076] 0.100 g (0.321 mmol) of 3-[2-(2,4-Dichlorophenyl)-ethoxy]-benzoic acid was dissolved in 2 ml of DMF and treated with 0.148 g (1.28 mmol) of N-NEM and 0.105 g (0.321 mmol) of TOTU and 0.0569 g (0.32 mmol) of 1-Pyridin-4-ylmethyl-piperazine. The solution was stirred for 16 h at RT. The solvent was removed under reduced pressure, the residue was taken-up in ethyl acetate and the solution was washed twice with saturated aqueous sodium bicarbonate and once with saturated aqueous sodium chloride. The organic phase was dried with magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with a gradient of 0-17% MeOH in DCM. Yield 84 mg. MS (ES^+): m/e = 470 (M^+).

Example 8: 3-[2-(2,4-Dich lorophenyl)-ethoxy]-N-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4- ylmethyl)-benzamide

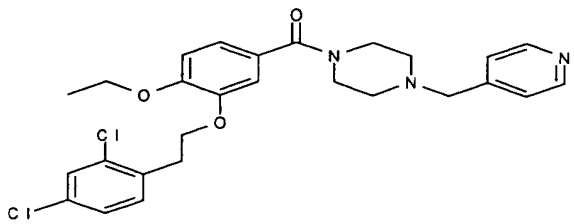
[0077]



0.100 g (0.321 mmol) of 3-[2-(2,4-Dichlorophenyl)-ethoxy]-benzoic acid was dissolved in 2 ml of DMF and treated with 0.148 g (1.28 mmol) of N-NEM and 0.105 g (0.321 mmol) of TOTU and 0.123 g (0.64 mmol) of C-(3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-yl)-methylamine. The solution was stirred for 16 h at RT. The solvent was removed under reduced pressure, the residue was taken-up in ethyl acetate and the solution was washed twice with saturated aqueous sodium bicarbonate and once with saturated aqueous sodium chloride. The organic phase was dried with magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with a gradient of 0 to 17% MeOH in DCM. Yield 73 mg. MS (ES^+): m/e = 484 (M^+).

Example 9: {3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-ethoxy-phenyl}-(4-pyridin-4-ylmethyl-piperazin-1- yl)-methanone

[0078]



(i) 4-Ethoxy-3-hydroxy-benzoic acid ethyl ester

[0079] 5 g (27.2 mmol) of 3,4-Dihydroxy-benzoic acid ethyl ester was dissolved in 100 ml DMF and 3.75g (27.2 mmol) of potassium carbonate was added. The solution was cooled to 0°C and a solution of 2.96g (27.2 mmol) ethyl bromide in 10 ml DMF was added dropwise. The solution was stirred for 16 h at room temperature (RT). The solvent was removed under reduced pressure. The residue was taken-up in ethyl acetate and the solution was washed three times with water and twice with saturated aqueous sodium chloride. The organic phase was dried with magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with ethyl acetate/n-heptane (1/4).
Yield 1.84g. MS (Cl^+): m/e = 211.1 $(M+H)^+$.

(ii) 3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-ethoxy-benzoic acid ethyl ester

[0080] 0.5 g (2.38 mmol) of 4-Ethoxy-3-hydroxy-benzoic acid ethyl ester was dissolved in 10 ml of anhydrous tetrahydrofuran. To this solution was added 0.5 g (2.62mmol) of 2-(2,4-Dichlorophenyl)-ethanol, 2.38 g (equivalent to 7.13 mmol PPh_3) of triphenylphosphine derivatized polystyrene and 1.24 g (7.13 mmol) of DEAD. The solution was shaken for 16 h at RT. The polymer was filtered off and washed with ethyl acetate. The solvent was removed under reduced pressure. The residue was taken-up in ethyl acetate and the solution was washed three times with water arid twice with saturated aqueous sodium chloride. The organic phase was dried with magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with ethyl acetate/n-heptane (1/4). Yield 300 mg. LC-MS (ES^+): m/e = 383 $(M)^+$

(iii) 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-ethoxy-benzoic acid

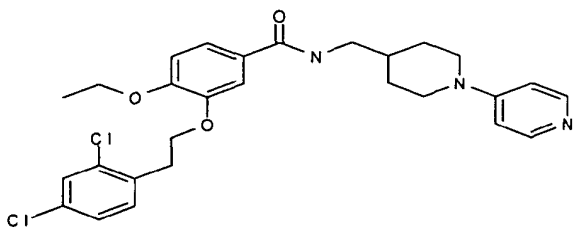
[0081] 0.300 g (0.78 mmol) of 3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-ethoxy-benzoic acid ethyl ester was dissolved in 10 ml of dioxan. 2N aqueous NaOH was added to the solution to give a pH of 13. The reaction solution was heated at 60°C for 10 h. 5 ml water was added, followed by concentrated hydrochloric acid to give a pH of 1-2, whereupon the product precipitated from solution. The suspension was stirred for 30min, then the product was filtered off and dried under reduced pressure.
Yield 0.205g. MS (Cl^+): m/e = 355 (M^+).

(iv) {3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-ethoxy-phenyl}-(4-pyridin-4-ylmethyl-piperazin-1-yl)-methanone

[0082] 0.050 g (0.141 mmol) of 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-ethoxy-benzoic acid was dissolved in 2 ml of DMF and treated with 0.065 g (0.564 mmol) of N-NEM and 0.046 g (0.141 mmol) of TOTU and 0.025 g (0.141 mmol) of 1-Pyridin-4-ylmethyl-piperazine. The solution was stirred for 16 h at RT. The solvent was removed under reduced pressure, the residue was taken-up in ethyl acetate and the solution was washed twice with saturated aqueous sodium bicarbonate and once with saturated aqueous sodium chloride. The organic phase was dried with magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residue was purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water(+0.01% trifluoroacetic acid). After lyophilization the product was obtained as its trifluoroacetate salt.
Yield 28.6 mg. MS (ES^+): m/e = 514 (M^+).

Example 10: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-ethoxy-N-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-benzam ide

[0083]

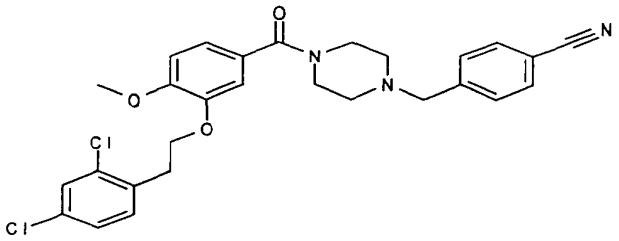


[0084] 0.050 g (0.141 mmol) of 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-ethoxy-benzoic acid was dissolved in 2 ml of

DMF and treated with 0.163 g (1.41 mmol) of N-NEM and 0.046 g (0.141 mmol) of TOTU and 0.075 g (0.141 mmol) of C-(3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-yl)-methylamine tris-trifluoroacetate salt. The solution was stirred for 16 h at RT. The solvent was removed under reduced pressure, the residue was taken-up in ethyl acetate and the solution was washed twice with saturated aqueous sodium bicarbonate and once with saturated aqueous sodium chloride. The organic phase was dried with magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residue was purified by preparative RP-HPLC eluting with a gradient of 0 to 100% acetonitrile in water (+0.01% trifluoroacetic acid). After lyophilization the product was obtained as its trifluoroacetate salt. Yield 26.1 mg. MS (ES+): m/e = 528 (M^+).

Example 11 : 4-(4-{3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-benzoyl}-piperazin-1-ylmethyl)- benzonitrile

[0085]



(i) 4-{3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methoxy-benzoyl}-piperazine-1-carboxylic acid tBu ester

[0086] 3 g (9 mmol) of 3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methoxy-benzoic acid was dissolved in 30 ml DMF and treated with 4.6 ml (36 mmol) of N-NEM and 3.2 g (9.9 mmol) of TOTU and 1.67g (9 mmol) of piperazine-1-carboxylic acid tBu ester. The solution was stirred for 40 min. at RT. The solvent was removed under reduced pressure, the residue was taken-up in DCM and the solution was washed three times with saturated aqueous sodium bicarbonate. The organic phase was dried with sodium sulfate, filtered and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with n-heptane/ethyl acetate (1/1).
Yield 4.2 g. MS (ES+): m/e = 509 (M^+).

(ii) {3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methoxy-phenyl}-piperazin-1-yl-methanone, hydrochloride salt

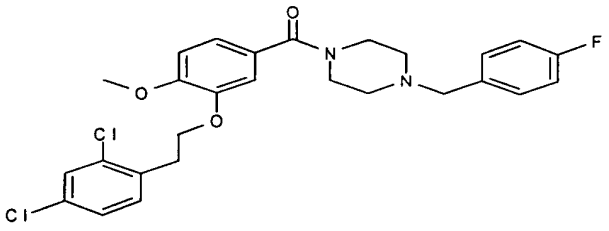
[0087] 4.2 g (8.2 mmol) of 4-{3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methoxy-benzoyl}-piperazine-1-carboxylic acid tBu ester was dissolved in 25 ml of MeOH. To this solution was added 100 ml of a saturated solution of HCl in MeOH. The solution was stirred for 30 min at RT. The solvent was removed under reduced pressure. The residue was treated twice with toluene, which was removed under reduced pressure.
Yield 3.8 g. MS (ES+): m/e = 409 (M^+).

(iii) 4-(4-{3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methoxy-benzoyl}-piperazin-1-ylmethyl)-benzonitrile

[0088] 0.050 g (0.112 mmol) of {3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methoxy-phenyl}-piperazin-1-yl-methanone, hydrochloride salt was dissolved in 3 ml of DMF. 61.9 mg (0.448mmol) of potassium carbonate was added to the solution, followed by 0.022 g (0.11 mmol) of 4-bromomethyl-benzonitrile. The reaction solution was shaken for 16 h at RT. The solvent was removed under reduced pressure, the residue was taken-up in ethyl acetate and the solution was washed twice with water and once with saturated aqueous sodium chloride. The organic phase was dried with magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with n-heptane/ethyl acetate (1/1), and DCM/MeOH (10/1).
Yield 33mg. MS (ES+): m/e = 524 (M^+).

Example 12: {3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methoxy-phenyl}-[4-(4-fluorobenzyl)-piperazin-1- yl]-methanone

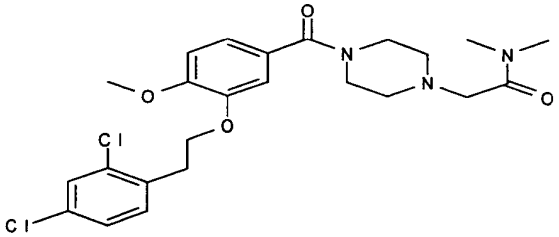
[0089]



[0090] 0.050 g (0.112 mmol) of {3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methoxy-phenyl}-piperazin-1-yl-methanone, hydrochloride salt was dissolved in 3 ml of DMF. 61.9 mg (0.448mmol) of potassium carbonate was added to the solution, followed by 0.021 g (0.11 mmol) of 1-Bromomethyl-4-fluoro-benzene. The reaction solution was shaken for 16 h at RT. The solvent was removed under reduced pressure, the residue was taken-up in ethyl acetate and the solution was washed twice with water and once with saturated aqueous sodium chloride. The organic phase was dried with magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with n-heptane/ethyl acetate (1/1), and DCM/MeOH (10/1).
Yield 42.5mg. MS (ES^+): m/e = 517 (M^+).

Example 13: 2-(4-{3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methoxy-benzoyl}-piperazin-1 -yl)-N,N- dimethyl-acetamide

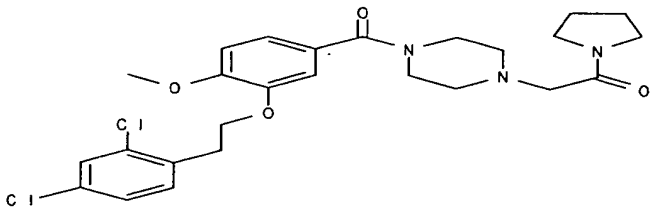
[0091]



[0092] 0.050 g (0.112 mmol) of {3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methoxy-phenyl}-piperazin-1-yl-methanone, hydrochloride salt was dissolved in 3 ml of DMF. 61.9 mg (0.448mmol) of potassium carbonate was added to the solution, followed by 0.016 g (0.13 mmol) of 2-chloro-N,N-dimethyl-acetamide. The reaction solution was shaken for 32 h at RT. The solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with a gradient of 0-17% MeOH in DCM, followed by additional purification by preparative RP-HPLC eluting with a gradient of 0 to 100% acetonitrile in water (+0.01% trifluoroacetic acid). After lyophilization the product was obtained as its trifluoroacetate salt. Yield 20.5mg. MS (ES^+): m/e = 494 (M^+).

Example 14: 2-(4-{3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methoxy-benzoyl}-piperazin-1-yl)-1-pyrrolidin-1-yl-ethanone

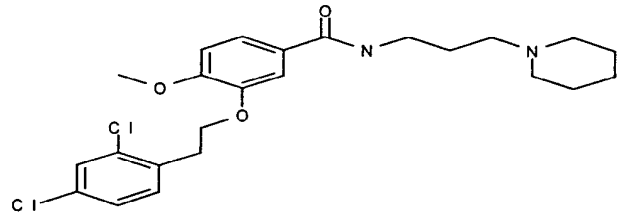
[0093]



[0094] 0.102 g (0.3 mmol) of 3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methoxy-benzoic acid was dissolved in 3 ml of DMF. 138.2 mg (1.2 mmol) of N-NEM and 0.098 g (0.3 mmol) TOTU were added to the solution, followed by 0.059 g (0.3 mmol) of2-piperazin-1-yl-1-pyrrolidin-1-yl-ethanone. The reaction solution was stirred for 4 h at RT. The solvent was removed under reduced pressure. The solvent was removed under reduced pressure, the residue was taken-up in ethyl acetate and the solution was washed three times with saturated aqueous sodium bicarbonate. The organic phase was dried with sodium sulfate, filtered and the solvent was removed under reduced pressure. The residue was purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). After lyophilization the product was obtained as its trifluoroacetate salt. Yield 74 mg. MS (ES^+): m/e = 520 (M^+).

Example 15: 3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methoxy-N-(3-piperidin-1-yl-propyl)-benzamide

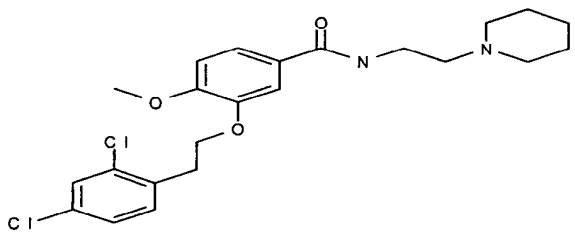
[0095]



[0096] 0.075 g (0.22 mmol) of 3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methoxy-benzoic acid was dissolved in 3 ml of DMF. 101.3 mg (0.88 mmol) of N-NEM and 0.072 g (0.22 mmol) TOTU were added to the solution, followed by 0.031 g (0.22 mmol) of 3-piperidin-1-yl-propylamine. The reaction solution was stirred for 4 h at RT. The solvent was removed under reduced pressure. The solvent was removed under reduced pressure, the residue was taken-up in ethyl acetate and the solution was washed three times with saturated aqueous sodium bicarbonate. The organic phase was dried with sodium sulfate, filtered and the solvent was removed under reduced pressure. The residue was purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). After lyophilization the product was obtained as its trifluoroacetate
salt. Yield 50 mg. MS (ES^+): m/e = 465 (M^+).

Example 16: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-(2-piperidin-1 -yl-ethyl)-benzamide

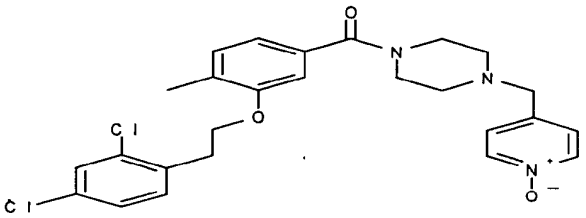
[0097]



[0098] 0.075 g (0.22 mmol) of 3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methoxy-benzoic acid was dissolved in 3 ml of DMF. 101.3 mg (0.88 mmol) of N-NEM and 0.072 g (0.22 mmol) TOTU were added to the solution, followed by 0.028 g (0.22 mmol) of 2-piperidin-1-yl-ethylamine. The reaction solution was stirred for 4 h at RT. The solvent was removed under reduced pressure. The solvent was removed under reduced pressure, the residue was taken-up in ethyl acetate and the solution was washed three times with saturated aqueous sodium bicarbonate. The organic phase was dried with sodium sulfate, filtered and the solvent was removed under reduced pressure. The residue was purified by preparative RP-HPLC eluting with a gradient of 0 to 100% acetonitrile in water (+0.01% trifluoroacetic acid). After lyophilization the product was obtained as its trifluoroacetate salt. Yield 50 mg. MS (ES^+): m/e = 451 (M^+).

Example 17: {3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methyl-phenyl}-[4-(1-oxy-pyridin-4-ylmethyl)- piperazin-1-yl]-methanone

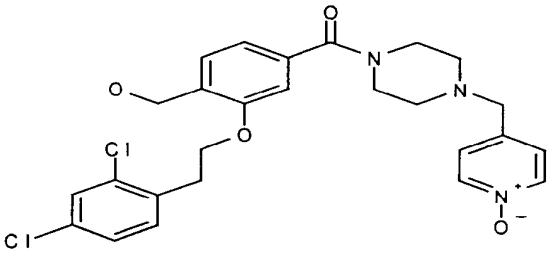
[0099]



[0100] 0.020 g (0.04 mmol) of {3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methyl-phenyl}-(4-pyridin-4-ylmethyl-piperazin-1-yl)-methanone was dissolved in 1 ml of DCM. To this solution was added 15.2 mg (0.06 mmol) meta-chloroperbenzoic acid. The reaction was stirred at RT for 16h, then the solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with a gradient of 0 to 17% MeOH in DCM. Yield 5 mg. MS (ES^+): m/e = 500 (M^+).

Example 18: {3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-hydroxymethyl-phenyl}-[4-(1 -oxypyridin-4-ylmethyl)- piperazin-1-yl]-methanone

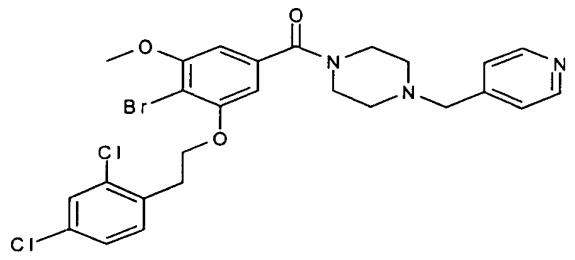
[0101]



[0102] This compound was isolated by chromatography from the reaction described for the synthesis of example 17. Yield 2 mg. MS (ES^+): m/e = 516 (M^+).

Example 19: {4-Bromo-3-[2-(2,4-dichlorophenyl)-ethoxy]-5-methoxyphenyl}-(4-pyridin-4-ylmethyl- piperazin-1-yl)-methanone

[0103]



(i) 4-Bromo-3-[2-(2,4-dichlorophenyl)-ethoxy]-5-methoxy-benzoic acid

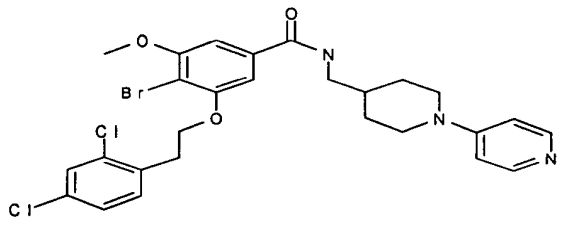
[0104] 0.2 g (0.49 mmol) of 4-Bromo-3-[2-(2,4-dichlorophenyl)-ethoxy]-5-hydroxy-benzoic acid was dissolved in 5 ml DMF and 0.272 mg (1.97 mmol) of potassium carbonate was added. The solution was cooled to 0°C and 0.699 g (4.9 mmol) methyl bromide was added. The solution was stirred for 16 h at RT. The solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with ethyl acetate/n-heptane (1/1). The resulting compound was dissolved in 10 ml dioxan and 1ml water. 2N aqueous NaOH was added to the solution to give a pH of 13. The reaction solution was heated at 60°C for 4 h. 5 ml water was added, followed by concentrated hydrochloric acid to give a pH of 1-2, whereupon the product precipitated from solution. The suspension was stirred for 30min, then the product was filtered off and dried under reduced pressure. Yield 120 mg. MS (ES^-): m/e = 416.9 $(M-H)^-$.

(ii) {4-Bromo-3-[2-(2,4-dichlorophenyl)-ethoxy]-5-methoxyphenyl}-(4-pyridin-4-ylmethyl-piperazin-1 -yl)-methanone

[0105] 0.05 g (0.119 mmol) of 4-Bromo-3-[2-(2,4-dichlorophenyl)-ethoxy]-5-methoxy-benzoic acid was dissolved in 2 ml of DMF and treated with 0.055 g (0.476 mmol) of N-NEM and 0.039 g (0.119 mmol) of TOTU and 0.021 g (0.12 mmol) of 1-Pyridin-4-ylmethyl-piperazine. The solution was stirred for 16 h at RT. The solvent was removed under reduced pressure, the residue was taken-up in acetonitrile and the residue was purified by preparative RP-HPLC eluting with a gradient of 0 to 100% acetonitrile in water (+0.01% trifluoroacetic acid). After lyophilization the product was obtained as its trifluoroacetate salt. Yield 35.5 mg. MS (ES^+): m/e = 578 $(M+H)^+$.

Example 20: 4-Bromo-3-[2-(2,4-dichloro-phenyl)-ethoxy]-5-methoxy-N-(3,4,5,6-tetrahydro-2H- [1,4']bipyridinyl-4-ylmethyl)-benzamide

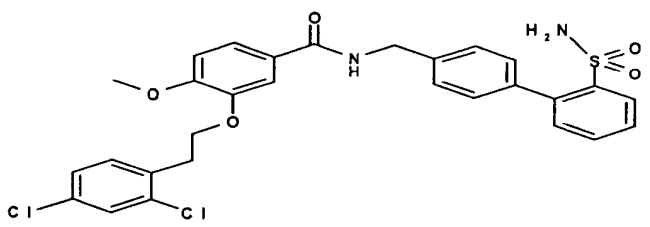
[0106]



[0107] 0.05 g (0.119 mmol) of 4-Bromo-3-[2-(2,4-dichlorophenyl)-ethoxy]-5-methoxy-benzoic acid was dissolved in 2 ml of DMF and treated with 0.055 g (0.476 mmol) of N-NEM and 0.039 g (0.119 mmol) of TOTU and 0.063 g (0.12 mmol) of C-(3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-yl)-methylamine tris-trifluoroacetate salt. The solution was stirred for 16 h at RT. The solvent was removed under reduced pressure, the residue was taken-up in acetonitrile and the residue was purified by preparative RP-HPLC eluting with a gradient of 0 to 100% acetonitrile in water (+0.01% trifluoroacetic acid). After lyophilization the product was obtained as its trifluoroacetate salt.
Yield 34.3 mg. MS (ES^+): m/e = 592 $(M+H)^+$.

Example 21: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-(2'-sulfamoyl-biphenyl-4-ylmethyl)- benzamide

[0108]



(i) 4'-Aminomethyl-biphenyl-2-sulfonic acid dimethylaminomethyleneamide

[0109] 1.5 g of 4'-formyl-biphenyl-2-sulfonic acid dimethylaminomethyleneamide prepared according to H. Jendralla et al. (Liebigs Ann. 1995, 1253-7) in 15 ml MeOH were treated with 208.6 mg $NaCNBH_3$ and the reaction was stirred for 4 hours at RT. The pH was adjusted to 4.0, the reaction was filtered, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel eluting with a gradient of 10-20% MeOH in DCM. Yield 912 mg. MS (ES^+): m/e = 318 ($M+H^+$).

(ii) 4'-Aminomethyl-biphenyl-2-sulfonic acid amide hydrochloride

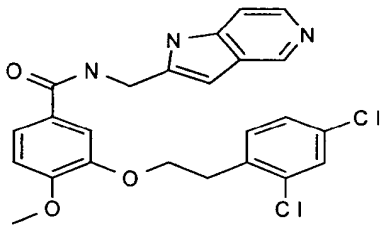
[0110] 400 mg of 4'-Aminomethyl-biphenyl-2-sulfonic acid dimethylaminomethyleneamide were treated with 10 ml MeOH and 4 ml conc. HCl and refluxed for 1h. Solvent and HCl were evaporated and the product used without purification.

(iii) 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-(2'-sulfamoyl-biphenyl-4-ylmethyl)-benzamide

[0111] 77 mg of 4'-aminomethyl-biphenyl-2-sulfonic acid amide hydrochloride were reacted with 100 mg of 3-[2-(2,4-dichloro-phenyl)-ethoxy]-4-methoxy-benzoic acid, 111 mg HATU and 0.2 ml DIPEA in 3 ml DMF for 1 h at RT. The pH was adjusted to 4.0, the solvent evaporated, the residue was dissolved in DCM and extracted with brine. After evaporation of the solvent, the product was purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid).
Yield: 33 mg. MS (ES^+): m/e = 585.1; 587.0 ($M+H^+$).

Example 22: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-benzamide

[0112]



(i) 3-Hydroxy-4-methoxy-benzoic acid methyl ester

[0113] 10 ml of thionyl chloride was added to 250 ml of MeOH at 0 °C. The solution was stirred for 10 min. and 25 g of 3-hydroxy-4-methoxybenzoic acid were added. The reaction was stirred for 16 h at RT then heated to 50 °C for 3 h. The solvents were removed under reduced pressure. The residue was directly used in the next reaction.

(ii) 3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methoxy-benzoic acid methyl ester

[0114] 20 g of triphenylphosphine and 10 g of 3-Hydroxy-4-methoxy-benzoic acid methyl ester were dissolved in 200 ml of anhydrous THF. The solution was cooled to 0 °C to 10 °C and a solution of 11.4 ml DEAD in 30 ml anhydrous THF was added dropwise over 20 min. The reaction was warmed to RT and stirred for 45 min. A solution of 11.3 ml 2-(2,4-Dichlorophenyl)-ethanol in 10 ml anhydrous THF was added with cooling. The reaction was stirred at RT for 16 h, then the solvents were removed under reduced pressure. The residue was treated with n-heptane:ethyl acetate/1:1. The filtrate was dried under reduced pressure. The product was purified by silica gel chromatography, eluting with n-heptane:ethyl acetate/4:1, then n-heptane:ethyl acetate/3:1. Yield 17g.

(iii) 3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methoxy-benzoic acid

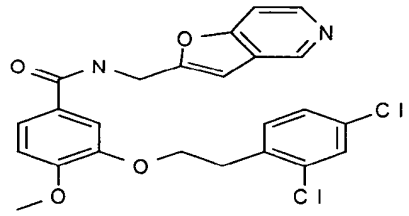
[0115] 17g of 3-[2-(2,4-Dichlorophenyl)-ethoxy]-4-methoxy-benzoic acid methyl ester was dissolved in 200ml of MeOH:water/3:1. 4.1g of lithium hydroxide monohydrate was added to the solution, and the reaction was stirred at RT for 16 h then at 90°C for 2 h. The solution was cooled to RT, then acidified with half-concentrated hydrochloric acid. The solvents were removed under reduced pressure and the residue was washed twice with warm water to remove salts. The so obtained acid was used for the subsequent reaction without further purification.

(iv) 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-benzamide

[0116] To a solution of 100 mg 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-benzoic acid in 1 ml DMF 53 mg carbonyldiimidazole were added. After stirring for 2 h at RT 48 mg of C-(1H-Pyrrolo[3,2-c]pyridin-2-yl)-methylamine tris-trifluoroacetate [prepared by adopting a procedure described by F. Ujjainwalla, D. Warner; Tertrahedron Lett. 1998, 39, 5355 and L. Xu, I. Lewis, S. Davidsen, J. Summers, Tertrahedron Lett. 1998, 39, 5159] were added and stirred over night after addition of 5 mg of DMAP. The solvent was removed under reduced pressure and the residue purified by preparative HPLC (C_{18} reverse phase column, elution with a H_2O/MeCN gradient with 0.5% TFA) The fractions containing the product were evaporated and lyophilized.
Yield 48 mg. MS (ESI+): 470, chloro pattern

Example 23: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-N-furo[3,2-c]pyridin-2-ylmethyl-4-methoxy- benzamide

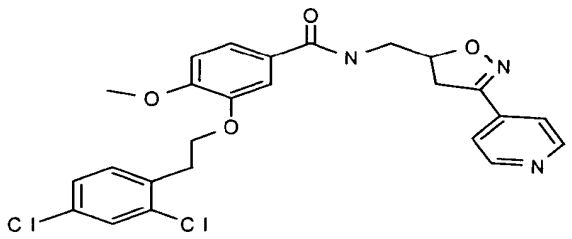
[0117]



[0118] The title compound was prepared analogously to Example 22 with the difference that C-Furo[3,2-c]pyridin-2-yl-methylamine [prepared by adopting a procedure described by F. Ujjainwalla, D. Warner; Tertrahedron Lett. **1998,** 39, 5355 and L. Xu, I. Lewis, S. Davidsen, J. Summers, Tertrahedron Lett. **1998,** 39, 5159] was used instead of C-(1H-Pyrrolo[3,2-c]pyridin-2-yl)-methylamine. MS (ESI+): 471, chloro pattern

Example 24: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-(3-pyridin-4-yl-4,5-dihydroisoxazol-5- ylmethyl)-benzamide

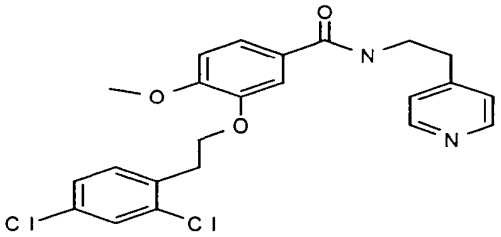
[0119]



[0120] The title compound was prepared analogously to Example 22 with the difference that C-(3-Pyridin-4-yl-4,5-dihydro-isoxazol-5-yl)-methylamine was used instead of C-(1 H-Pyrrolo[3,2-c]pyridin-2-yl)-methylamine. MS (ESI+): 500, chloro pattern

Example 25: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-(2-pyridin-4-yl-ethyl)-benzamide

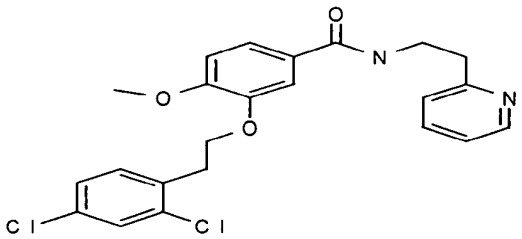
[0121]



[0122] The title compound was prepared analogously to Example 22 with the difference that 2-Pyridin-4-yl-ethylamine was used instead of C-(1H-Pyrrolo[3,2-c]pyridin-2-yl)-methylamine. MS (ESI+): 445, chloro pattern

Example 26: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-(2-pyridin-2-yl-ethyl)-benzamide

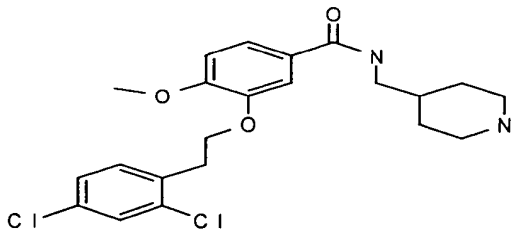
[0123]



[0124] The title compound was prepared analogously to Example 22 with the difference that 2-Pyridin-2-yl-ethylamine was used instead of C-(1 H-Pyrrolo[3,2-c]pyridin-2-yl)-methylamine. MS (ESI+): 445, chloro pattern

Example 27: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-piperidin-4-ylmethylbenzamide

[0125]



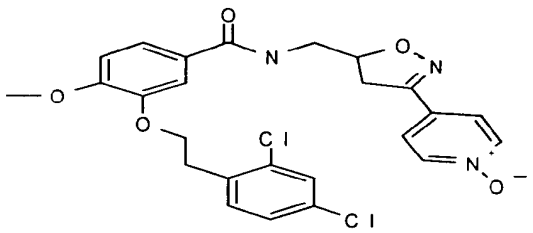
[0126] To a solution of 3 g 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-benzoic acid in 20 ml CH_2Cl_2 4.5 ml N-NEM and subsequently 2.9 g TOTU were added. After stirring for 1 h at RT 2.8 g 4-Aminomethyl-piperidine-1-carboxylic acid tBu ester in 10 ml CH_2Cl_2 were added and the mixture was stirred for 2 h. The reaction mixture was then diluted with 50 ml CH_2Cl_2 and was washed with saturated aqueous $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4. After removal of the solvent the white residue was recrystallized from ethyl acetate to yield 4.8 g of the BOC-protected derivative. This crystalline white solid was suspended in EtOH/HCl at RT. After 3 h a clear solution was obtained. Removal of the solvent under reduced pressure yielded a white foam.Yield: 3.7g

MS (ESI+) 437, chloro pattern

[0127] Alternatively the compound could be obtained by activation with carbonylimidazole and subsequent reaction of the activated intermediate with C-Piperidin-4-yl-methylamine.

Example 28: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-N-[3-(1-hydroxy-pyridin-4-yl)-4,5-dihydro-isoxazol-5- ylmethyl]-4-methoxy-benzamide

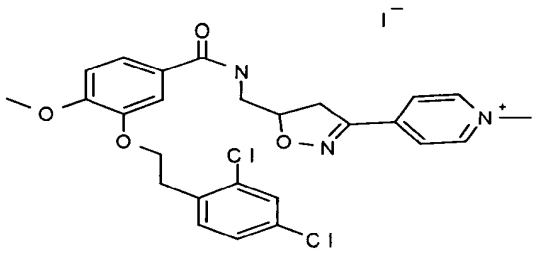
[0128]



[0129] To a solution of 100 mg 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-(3-pyridin-4-yl-4,5-dihydro-isoxazol-5- ylmethyl)-benzamide in 5 ml CH_2Cl_2 70 mg MCPBA were added at RT and stirred over night. The solvent was removed under reduced pressure and the residue purified by preparative HPLC (C_{18} reverse phase column, elution with a H_2O/MeCN gradient with 0.5 % TFA) The fractions containing the product were evaporated and lyophilized. Yield: 50 mg MS (ESI+): 516, chloro pattern

Example 29: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-N-[3-(1-methyl-pyridin-4-ium)-4,5-dihydro-isoxazol-5- ylmethyl]-4-methoxy-benzamidyl iodide

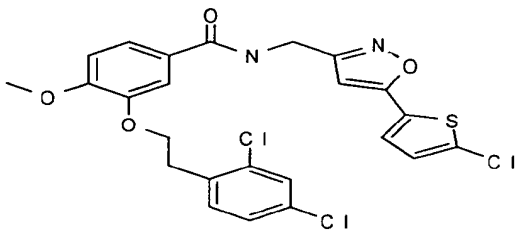
[0130]



[0131] To a solution 30 mg (0.06 mmol) 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-(3-pyridin-4-yl-4,5-dihydro-isoxazol-5- ylmethyl)-benzamide in 5 ml acetone 0.3 ml MeI were added at RT and stirred for 2 d. The product precipitated from the solution as a yellow solid which was isolated by filtration.
Yield. 25mg MS (ESI+): 515, chloro pattern

Example 30: N-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-[2-(2,4-dichlorophenyl)-ethoxy]-4- methoxy-benzamide

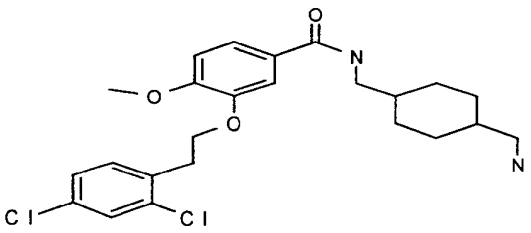
[0132]



[0133] To a solution of 250 mg hexamethylenetetraamine (1.8 mmol) in 8 ml $CHCl_3$ 500mg (1.8 mmol) 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole [prepared by adopting a procedure described by T.S. Gardner et al., *J. Org. Chem.* **1961,** 26, 1514 and Taguchi, Minoru; Okubo, Taketoshi; Yoshimura, Misa; Hatada, Yuchi; Ota, Tomoki; Tomizawa, Kazuyuki, Jpn. Kokai Tokkyo Koho (1997), 7 pp. CODEN: JKXXAF JP 09227557A2 19970902 Heisei.] were added and the reaction mixture stirred at 50 °C for 1 h and kept for additional 3 h at RT. The solvent was removed under reduced pressure and the residue was taken up in 5 ml EtOH and 2 ml concentrated HCl. This solution was heated for 5 h at 50 °C and the precipitate collected by filtration. An aliquot (68 mg) of the obtained amine was then subsequently coupled with 100 mg (0.29 mmol) 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-benzoic acid preactivated by addition of 95 mg TOTU and 150 mg N-NEM in 2 ml CH_2Cl_2. After stirring over night at RT the solvent was removed under reduced pressure an taken up in 3 ml sat. $NaHCO_3$ solution and filtered through a chem elut® cartridge by elution with ethyl acetate. After concentration under reduced pressure and purification by preparative HPLC (C_{18} reverse phase column, elution with a H_2O/MeCN gradient with 0.5% TFA) the fractions containing the product were evaporated and lyophilized.
Yield 10 mg MS (ESI+): 537, chloro pattern

Example 31: N-(4-Aminomethyl-cyclohexylmethyl)-3-[2-(2,4-dichloro-phenyl)-ethoxy]-4-methoxy- benzamide

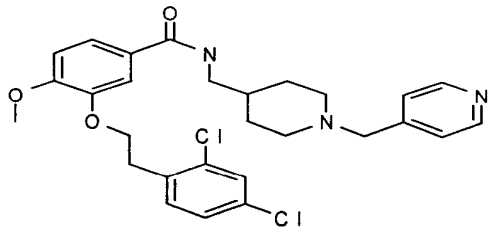
[0134]



[0135] To a solution of 100 mg 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-benzoic acid in 2 ml CH_2Cl_2 150 µl N-NEM and subsequently 96 mg TOTU were added. After stirring for 1 h at room temperature (RT) 83mg C-(4-Aminomethyl-cyclohexyl)-methylamine in 1 ml CH_2Cl_2 were added and the mixture was stirred for additional 2 h followed by removal of the solvent under reduced pressure. The residue was taken up in 3 ml sat. $NaHCO_3$ solution and filtered through a chem elut® cartridge by elution with ethyl acetate. After concentration under reduced pressure and purification by preparative HPLC (C_{18} reverse phase column, elution with a H_2O/MeCN gradient with 0.5 % TFA) the fractions containing the product were evaporated and lyophilized.
Yield: 32 mg MS (ESI+): 465, chloro pattern

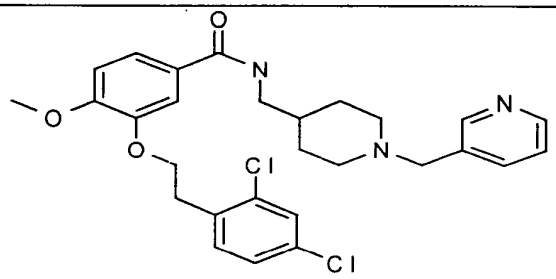
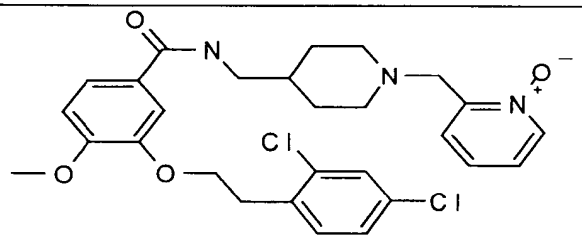
Example 32: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-(1-pyridin-4-ylmethylpiperidin-4- ylmethyl)-benzamide

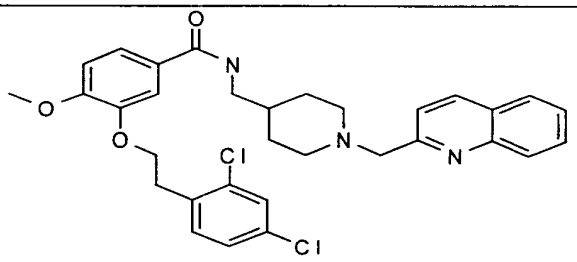
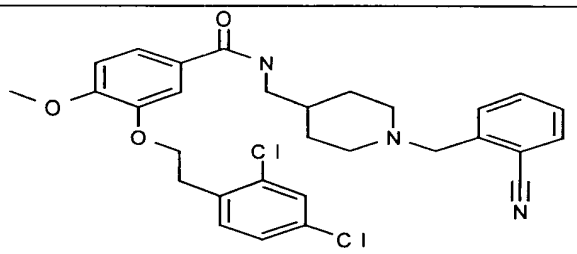
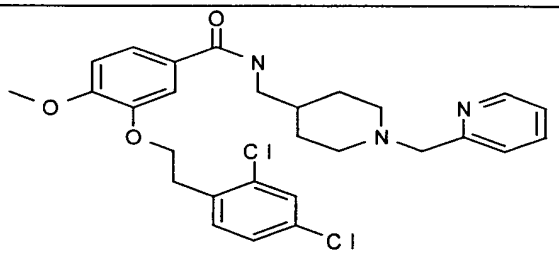
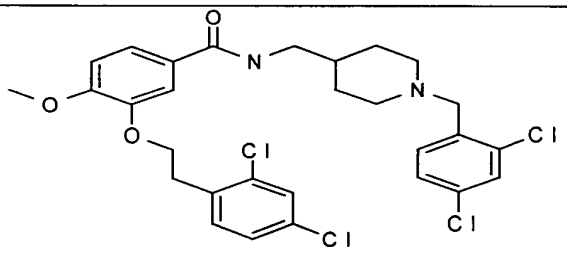
[0136]



[0137] A suspension of 120 mg 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-piperidin-4-ylmethyl-benzamide, 50 mg 4-Picolylchloride hydrochloride and 110 mg Cs_2CO_3 in 2 ml DMF was stirred at RT over night. The reaction mixture was diluted with 2 ml water, filtered through a chem elut® cartridge by elution with ethyl acetate. After concentration under reduced pressure and purification by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.5% TFA) the fractions containing the product were evaporated and lyophilized.
Yield 22 mg MS (ESI+): 528, chloro pattern

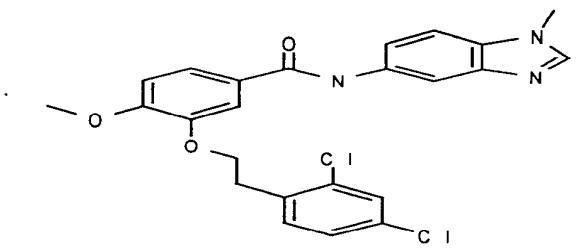
[0138] Analogously to example 32 the following compounds were prepared by a similar procedure

Example	Structure	MS (ESI+)
33		527, chloro pattern
34		544, chloro pattern

35		578, chloro pattern
36		552, chloro pattern
37		527, chloro pattern
38		595, chloro pattern

Example 39: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-(1-methyl-1H-benzoimidazol-5-yl)- benzamide

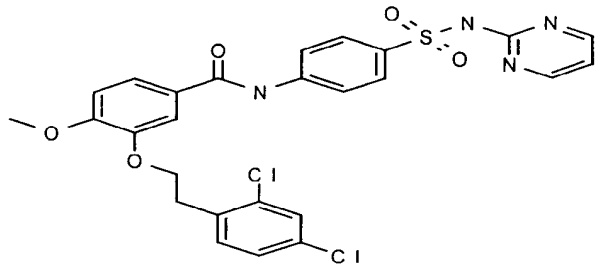
[0139]



[0140] This compound was prepared analogously to example 31 employing 1-Methyl-1H-benzoimidazol-5-ylamine as amine component. MS (ESI+): 470, chloro pattern

Example 40: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-[4-(pyrimidin-2-ylsulfamoyl)-phenyl]- benzamide

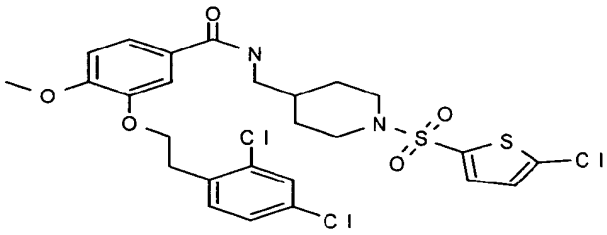
[0141]



[0142] To a solution of 100 mg 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-benzoic acid in 2 ml CH_2Cl_2 150 µl TEA and subsequently 77 mg TFFH were added. After stirring for 1 h at RT 87 mg 4-Amino-N-pyrimidin-2-yl-benzenesulfonamide in 1 ml CH_2Cl_2 were added and the mixture was stirred over night followed by removal of the solvent under reduced pressure. The residue was taken up in 3 ml sat. $NaHCO_3$ solution and filtered through a chem elut® cartridge by elution with ethyl acetate. After concentration under reduced pressure and purification by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.5% TFA) the fractions containing the product were evaporated and lyophilized. Yield 11 mg MS (ESI+): 573, chloro pattern

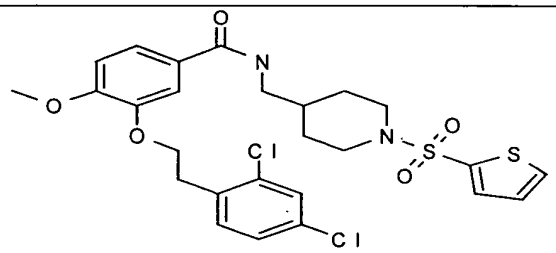
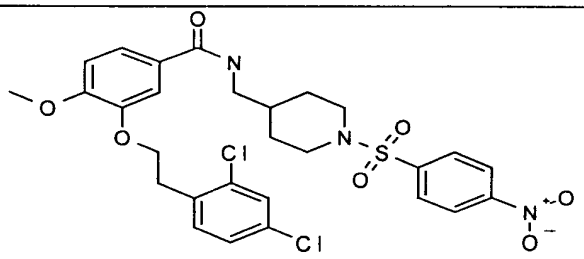
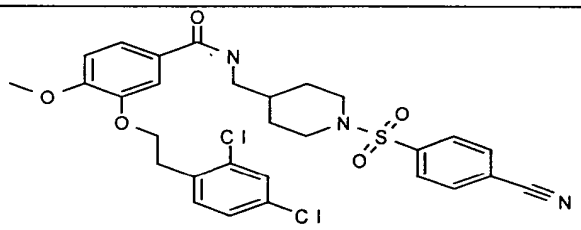
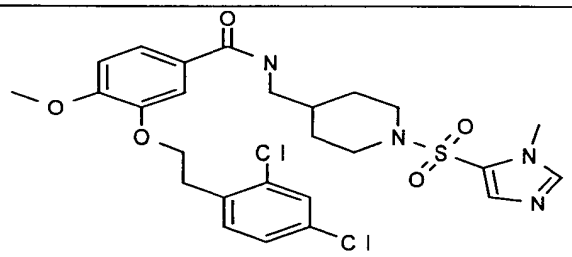
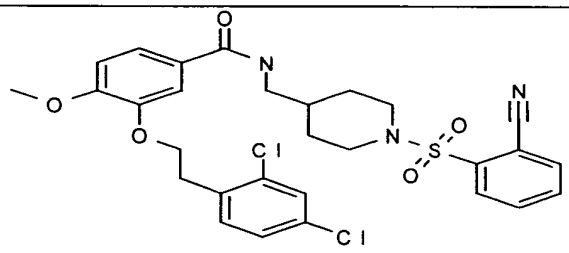
Example 41: N-[1-(5-Chloro-thiophene-2-sulfonyl)-piperidin-4-ylmethyl]-3-[2-(2,4-dichloro-phenyl)- ethoxy]-4-methoxy-benzamide

[0143]



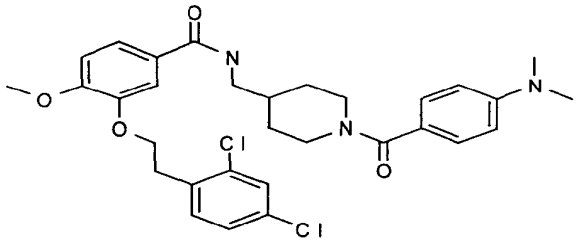
[0144] To a solution of 50 mg (0.14 mmol) 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-piperidin-4-ylmethyl-benzamide and 200 µl TEA in 3 ml DMF/CH_2Cl_2 1:2, 73 mg 5-Chloro-thiophene-2-sulfonyl chloride were added at RT. The reaction mixture was stirred over night followed by concentration under reduced pressure The residue was taken up 1 ml (0.5M) NaOH solution and filtered through a chem elut® cartridge by elution with ethyl acetate. After concentration under reduced pressure and purification by preparative HPLC (C_{18} reverse phase column, elution with a H_2O/MeCN gradient with 0.5% TFA) the fractions containing the product were evaporated and lyophilized.
Yield: 15mg MS (ESI+): 617, chloro pattern

[0145] Analogously to example 42 the following compounds were prepared by a similar procedure:

Example	Structure	MS (ESI+)
43		583, chloro pattern
44		624, chloro pattern
45		602, chloro pattern
46		581, chloro pattern
47		602, chloro pattern

Example 48: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-N-[1 -(4-dimethylamino-benzoyl)-piperidin-4-ylmethyl]- 4-methoxy-benzamide

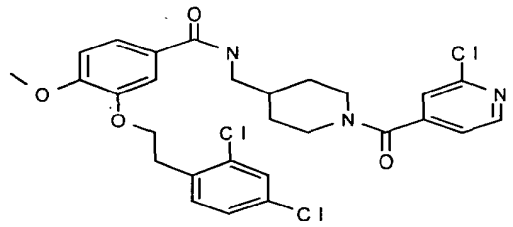
[0146]



[0147] To a solution of 50 mg (0.14 mmol) 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-piperidin-4-ylmethyl-benzamide and 200 µl TEA in 3 ml DMF/CH_2Cl_2 1:2, 61mg 4-Dimethylamino-benzoyl chloride hydrochloride were added at RT. The reaction mixture was stirred over night followed by concentration under reduced pressure The residue was taken up in 1 ml (0.5M) NaOH solution and filtered through a chem elut® cartridge by elution with ethyl acetate. After concentration under reduced pressure and purification by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.5% TFA) the fractions containing the product were evaporated and lyophilized.
Yield: 10mg MS (ESI+): 584, chloro pattern

Example 49: N-[1-(2-Chloro-pyridine-4-carbonyl)-piperidin-4-ylmethyl]-3-[2-(2,4-dichlorophenyl)- ethoxy]-4-methoxy-benzamide

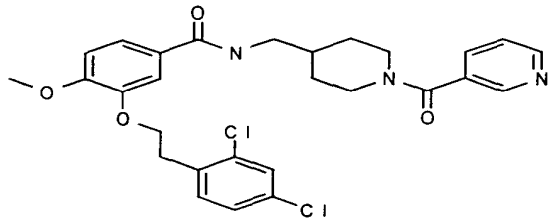
[0148]



[0149] The title compound was prepared analogously to example 48 employing 2-Chloroisonicotinoyl chloride hydrochloride as acylation component.
MS (ESI+): 576, chloro pattern

Example 50: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-[1-(pyridine-3-carbonyl)-piperidin-4- ylmethyl]-benzamide

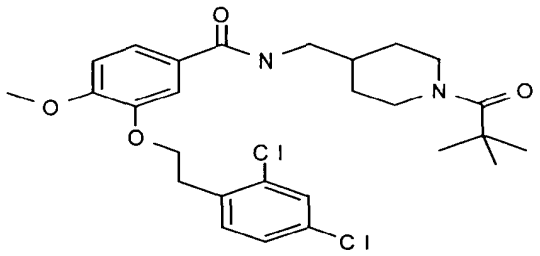
[0150]



[0151] The title compound was prepared analogously to example 48 employing Nicotinoyl chloride hydrochloride as acylation component. MS (ESI+): 542, chloro pattern

Example 51: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-N-[1-(2,2-dimethyl-propionyl)-piperidin-4-ylmethyl]- 4-methoxy-benzamide

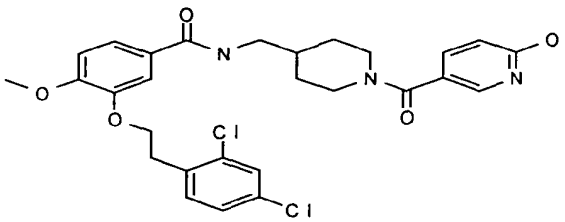
[0152]



[0153] This compound was prepared analogously to example 48 employing pivalic anhydride as acylation component. MS (ESI+): 521, chloro pattern

Example 52: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-N-[1 -(6-hydroxy-pyridine-3-carbonyl)-piperidin-4- ylmethyl]-4-methoxy-benzamide

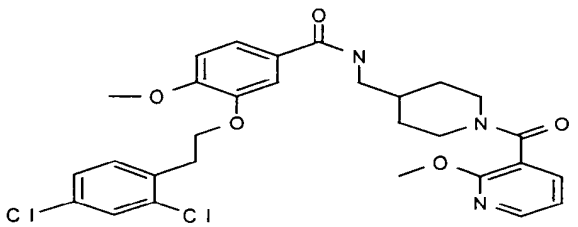
[0154]



[0155] To a solution of 100 mg 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-piperidin-4-ylmethyl-benzamide in 2 ml CH_2Cl_2 150µl N-NEM and subsequently 150 mg TOTU were added. After stirring for 1 h at RT 70 mg 6-Hydroxy-nicotinic acid in 1 ml CH_2Cl_2 were added and the mixture was stirred for additional 2 h followed by removal of the solvent under reduced pressure. The residue was taken up in 3 ml sat. $NaHCO_3$ solution and filtered through a chem elut® cartridge by elution with ethyl acetate. After concentration under reduced pressure and purification by preparative HPLC (C_{18} reverse phase column, elution with a H_2O/MeCN gradient with 0.5 % TFA) the fractions containing the product were evaporated and lyophilized.
Yield: 45mg MS (ESI+): 558, chloro pattern

Example 53: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-[1-(2-methoxy-pyridine-3-carbonyl)- piperidin-4-ylmethyl]-benzamide

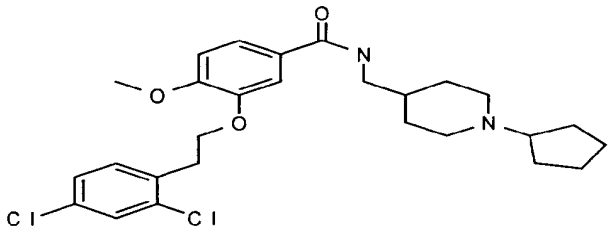
[0156]



[0157] The title compound was prepared analogously to example 52 employing 2-Methoxynicotinic acid as acylation component MS (ESI+): 572, chloro pattern

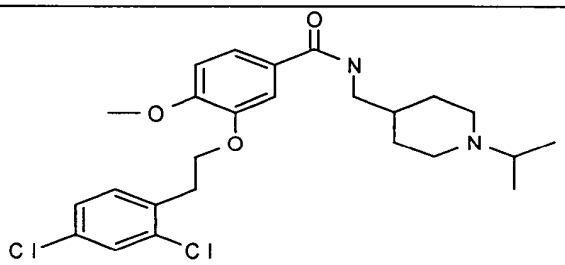
Example 54: N-(1-Cyclopentyl-piperidin-4-ylmethyl)-3-[2-[2,4-dichloro-phenyl)-ethoxy]-4-methoxy- benzamide

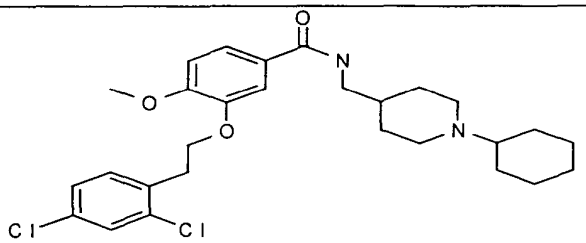
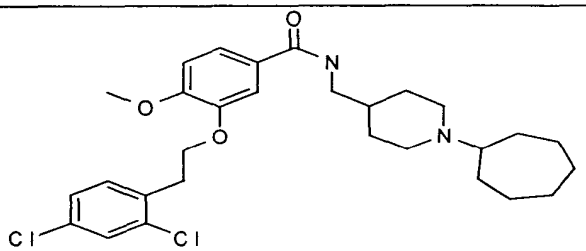
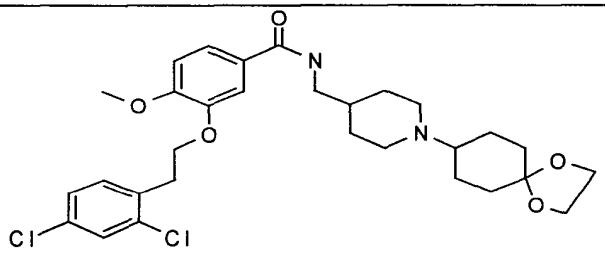
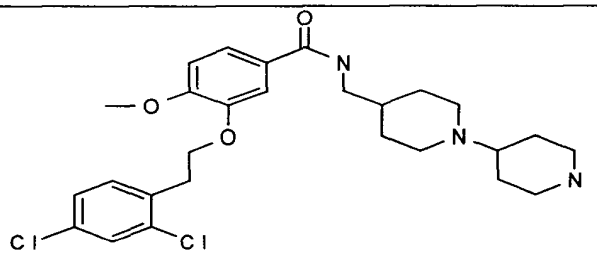
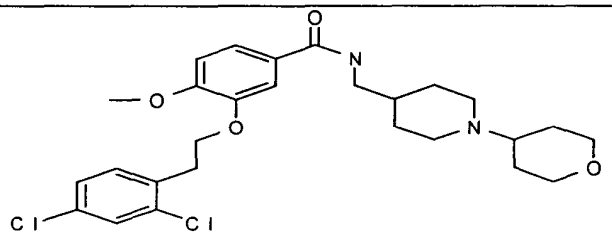
[0158]



[0159] To a solution of 100 mg 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-piperidin-4-ylmethyl-benzamide and 35 mg cyclopentanone in 2 ml acetonitrile 27 mg $Na(CN)BH_3$ were introduced. After stirring at RT overnight the reaction mixture was heated to 80°C for 4 h. After removal of the solvent under reduced pressure and purification by preparative HPLC (C_{18} reverse phase column, elution with a H_2O/MeCN gradient with 0.5% TFA) the fractions containing the product were evaporated and lyophilized.
Yield: 47 mg MS (ESI+): 505, chloro pattern

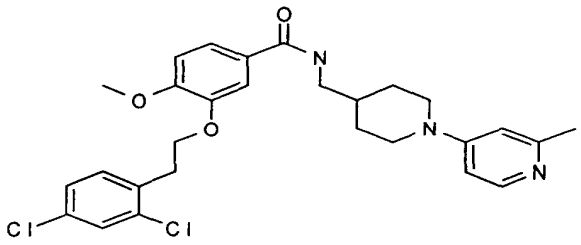
[0160] Analogously to example 54 the following compounds were prepared by a similar procedure:

Example	Structure	MS (ESI+)
55		479, chloro pattern

56		519, chloro pattern
57		533, chloro pattern
58		577, chloro pattern
59		520, chloro pattern
60		521, chloro pattern

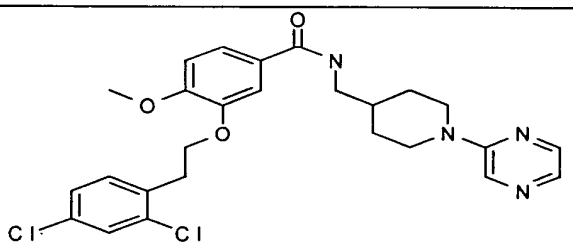
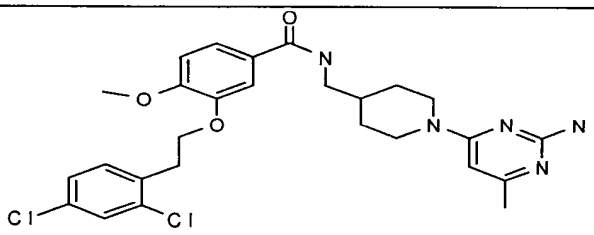
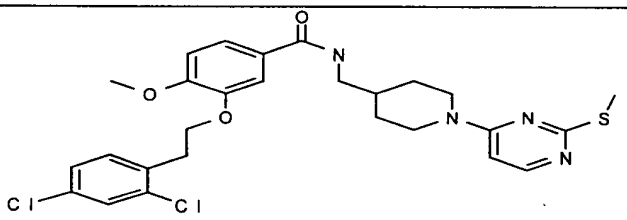
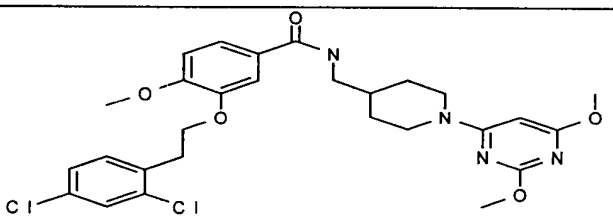
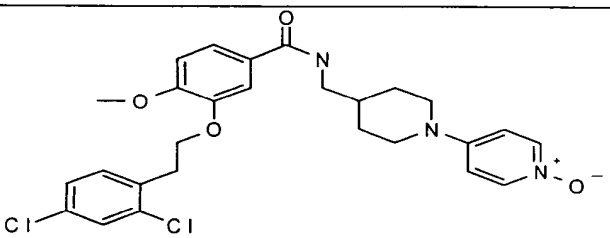
Example 61: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-(2'-methyl-3,4,5,6-tetrahydro-2H- [1,4']bipyridinyl-4-ylmethyl)-benzamide

[0161]



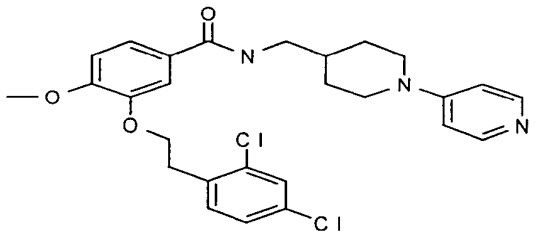
[0162] A solution of 100 mg 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-piperidin-4-ylmethyl-benzamide and 60 mg 4-Chloro-2-picoline in 6 ml n-BuOH/NEt_3 5:1 was refluxed overnight. After subsequent removal of the solvent under reduced pressure and purification by preparative HPLC (C_{18} reverse phase column, elution with a H_2O/MeCN gradient with 0.5 % TFA) the fractions containing the product were evaporated and lyophilized. Yield: 67 mg MS (ESI+): 528, chloro pattern

Analogously to example 61 the following compounds were prepared by a similar procedure:

Example	Structure	MS (ESI+)
62		515, chloro pattern
63		544, chloro pattern
64		561, chloro pattern
65		575, chloro pattern
66		530, chloro pattern

Example 67: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-benzamide

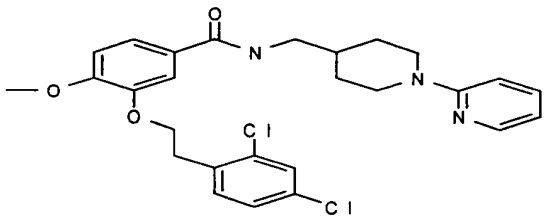
[0163]



[0164] A mixture of 110 mg (0.25 mmol) 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-piperidin-4-ylmethyl-benzamide, 49 mg (0.49 mmol) 4-Bromopyridine hydrochloride, 57 mg sodium-t-butoxide in 5 ml THF were purged with argon for 10 min. Then 15 mg of (+)-R-Binap and 15 mg $Pd(OAc)_2$ were added under argon and the mixture refluxed overnight. The residue was taken up in 3 ml saturated $NaHCO_3$ solution and filtered through a chem elut® cartridge by elution with ethyl acetate. Subsequent removal of the solvent under reduced pressure and purification by preparative HPLC (C_{18} reverse phase column, elution with a H_2O/MeCN gradient with 0.5% TFA) the fractions containing the product were evaporated and lyophilized.
Yield: 35 mg MS (ESI+): 514, chloro pattern

Example 68: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-benzamide

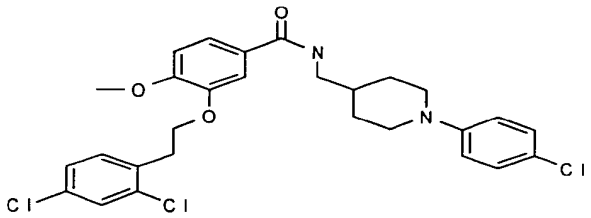
[0165]



[0166] This compound was prepared analogously to example 67 employing 2-Bromopyridine hydrochloride coupling component. MS (ESI+): 514, chloro pattern

Example 69: N-[1-(4-Chloro-phenyl)-piperidin-4-ylmethyl]-3-[2-(2,4-dichloro-phenyl)-ethoxy]-4- methoxy-benzamide

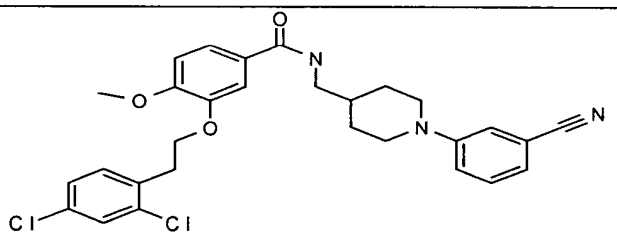
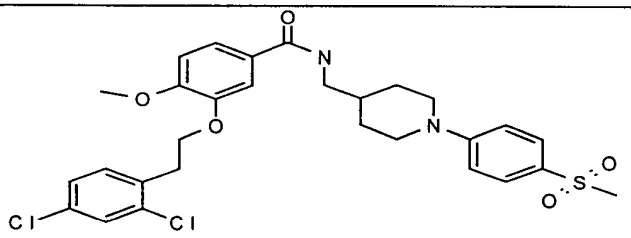
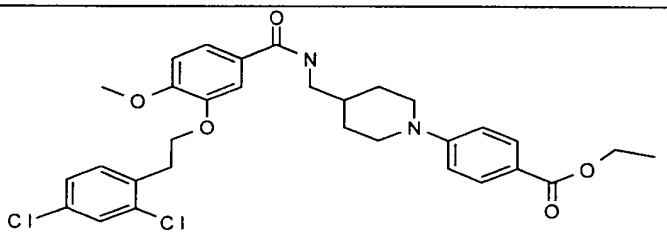
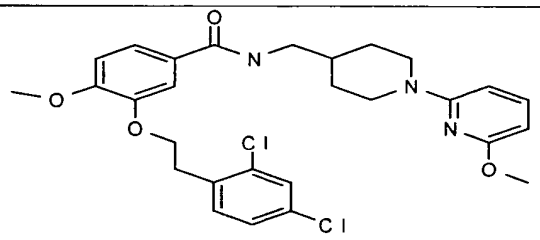
[0167]



[0168] A mixture of 100 mg (0.2 mmol) 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-piperidin-4-ylmethyl-benzamide, 66 mg (0.34 mmol) 4-Bromochlorobenzene, 33 mg sodium-t-butoxide in 5 ml THF were purged with argon for 10min. Then 37 mg of dppf and 5 mg $Pd(OAc)_2$ were added under argon and the mixture refluxed overnight. The residue was taken up in 3 ml sat. $NaHCO_3$ solution and filtered through a chem elut® cartridge by elution with ethyl

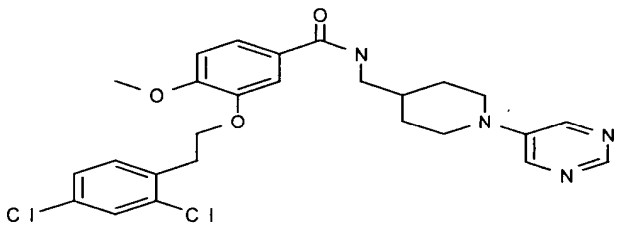
acetate. Subsequent removal of the solvent under reduced pressure and purification by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.5% TFA) the fractions containing the product were evaporated and lyophilized. Yield: 47 mg MS (ESI+): 547, chloro pattern

[0169] Analogously to example 69 the following compounds were prepared by a similar procedure:

Example	Structure	MS (ESI+)
70		538, chloro pattern
71		591, chloro pattern
72		585, chloro pattern
73		544, chloro pattern

Example 74: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-(1 -pyrimidin-5-yl-piperidin 4-ylmethyl)- benzamide

[0170]

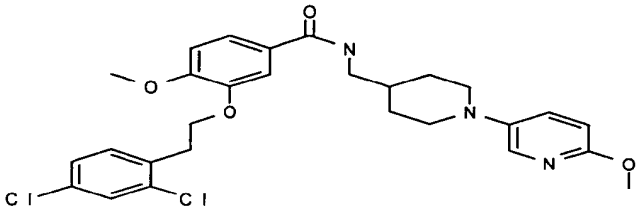


[0171] A mixture of 100 mg (0.2 mmol) 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-piperidin-4-ylmethyl-benza-

mide, 50 mg (0.32 mmol) 4-Brompyrimidine, 70 mg sodium-t-butoxide in 5 ml dioxane were purged with argon for 10 min. Then 37 mg of 2-(Dicyclohexylphosphino)biphenyl and 20 mg $Pd_2(dba)_3$ were added under argon and the mixture refluxed overnight. The residue was taken up in 3 ml saturated $NaHCO_3$ solution and filtered through a chem elut® cartridge by elution with ethyl acetate. Subsequent removal of the solvent under reduced pressure and purification by preparative HPLC (C_{18} reverse phase column, elution with a H_2O/MeCN gradient with 0.5 % TFA) the fractions containing the product were evaporated and lyophilized.
Yield: 21 mg MS (ESI+): 515, chloro pattern

Example 75: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-(6'-methoxy-3,4,5,6-tetrahydro-2H- [1,3']bipyridinyl-4-ylmethyl)-benzamide

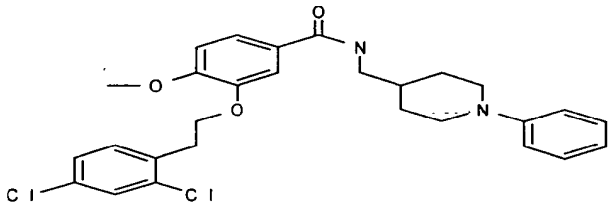
[0172]



[0173] A mixture of 100 mg (0.2 mmol) 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-piperidin-4-ylmethyl-benzamide, 55 mg (0.32 mmol) 5-Brom-2-methoxypyridine, 70 mg sodium-t-butoxide in 5 ml dioxane were purged with argon for 10min. Then 37 mg of 2-(Dicyclohexylphosphino)biphenyl and 20 mg $Pd_2(dba)_3$ were added under argon and the mixture refluxed overnight. The residue was taken up in 3 ml sat. $NaHCO_3$ solution and filtered through a chem elut® cartridge by elution with ethyl acetate. Subsequent removal of the solvent under reduced pressure and purification by preparative HPLC (C_{18} reverse phase column, elution with a H_2O/MeCN gradient with 0.5 % TFA) the fractions containing the product were evaporated and lyophilized.
Yield: 52 mg MS (ESI+): 544, chloro pattern

Example 76: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-(1-phenyl-piperidin-4-ylmethyl)- benzamide

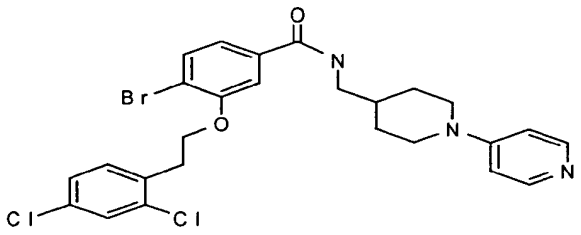
[0174]



[0175] A mixture of 100 mg (0.2 mmol) 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methoxy-N-piperidin-4-ylmethyl-benzamide, 50 mg (0.32 mmol) Bromobenzene, 70 mg sodium-t-butoxide in 5 ml dioxane were purged with argon for 10 min. Then 37 mg of 2-(Dicyclohexylphosphino)biphenyl and 20 mg $Pd_2(dba)_3$ were added under argon and the mixture refluxed overnight. The residue was taken up in 3 ml sat. $NaHCO_3$ solution and filtered through a chem elut® cartridge by elution with ethyl acetate. Subsequent removal of the solvent under reduced pressure and purification by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.5% TFA) the fractions containing the product were evaporated and lyophilized.
Yield: 14 mg MS (ESI+): 513, chloro pattern

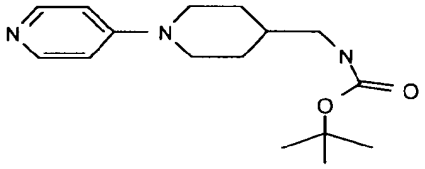
Example 77: 4-Bromo-3-[2-(2,4-dichloro-phenyl)-ethoxy]-N-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl- 4-ylmethyl)-benzamide

[0176]



(i) (3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-carbamic acid tBu ester

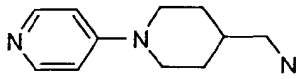
[0177]



[0178] A suspension of 5 g (23.3 mmol) piperidin-4-ylmethyl-carbamic acid tBu ester 3.85 g (25.7 mmol) 4-chloro-pyridin hydrochloride in 15 ml n-BuOH/H_2O/NEt_3 1:1:1 was refluxed for 3 days. After removal of the solvent under reduced pressure the residue was purified by chromatography on silica with CH_2Cl_2/MeOH 100:1 → 50:1 →10:1 - 5: 1 to yield a white solid.

(ii) C-(3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-yl)-methylamine tris trifluoroacetate

[0179]



[0180] To a solution of 4.58 g (3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-carbamic acid tBu ester in 12 ml $CH_2Cl_2$12 ml TFA were added at RT. After stirring for 30 min the solution was diluted with 20 ml of toluene and evaporated under reduced pressure. The residue was codestilled twice with toluene and then used in the subsequent reactions without futher purification.

(iii) 4-Bromo-3-hydroxy-benzoic acid methyl ester

[0181] 1.5 ml of thionyl chloride was added to 40 ml of MeOH at 0 °C. The solution was stirred for 10 min and 5 g of 4-Bromo-3-hydroxy-benzoic acid were added. The reaction was stirred for 16 h at RT then heated to 50 °C for 3 h. The solvents were removed under reduced pressure. The residue was used directly in the next step. Yield 5.92g

(iv) 4-Bromo-3-[2-(2,4-dichloro-phenyl)-ethoxy]-benzoic acid methyl ester

[0182] 1.6 g of triphenylphosphine and 1 g of 4-Bromo-3-hydroxy-benzoic acid methyl ester were dissolved in 15 ml of anhydrous THF. The solution was cooled to 0°C to 10°C and a solution of 0.88 ml DEAD in 5 ml anhydrous THF was added dropwise over 20 min. The reaction was warmed to RT and stirred for 45 min. A solution of 0.69 ml 2-(2,4-Dichlorophenyl)-ethanol in 2 ml anhydrous THF was added with cooling. The reaction was stirred at RT for 3 h,

then the solvents were removed under reduced pressure. The residue was treated with n-heptane:ethyl acetate/1:1. The filtrate was dried under reduced pressure. The product was purified by silica gel chromatography, eluting with n-heptane:ethyl acetate/4:1to n-heptane:ethyl acetate/1:1. Yield 2g.

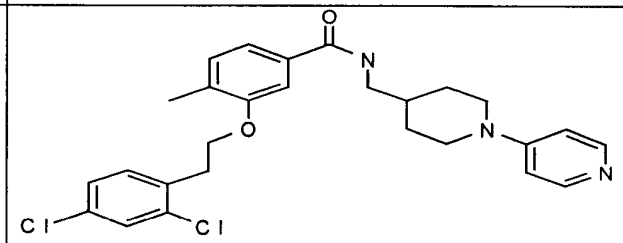
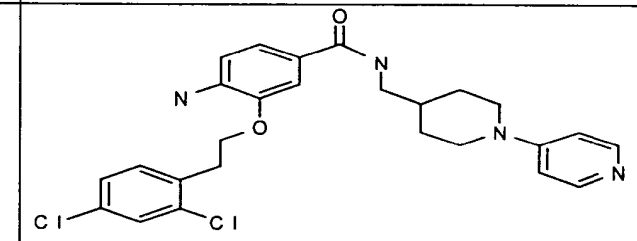
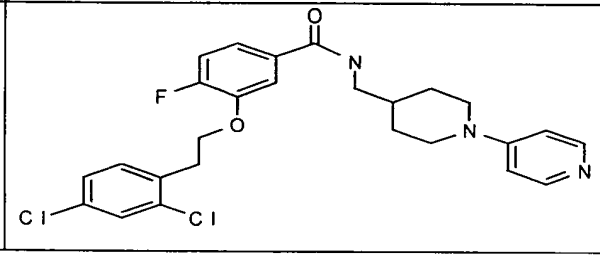
(v) 4-Bromo-3-[2-(2,4-dichloro-phenyl)-ethoxy]-benzoic acid

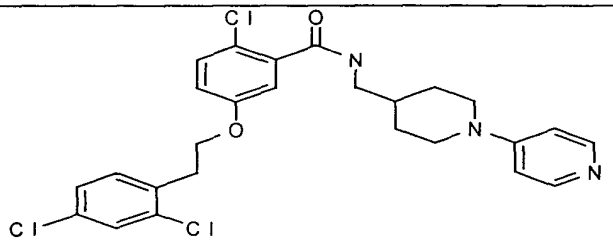
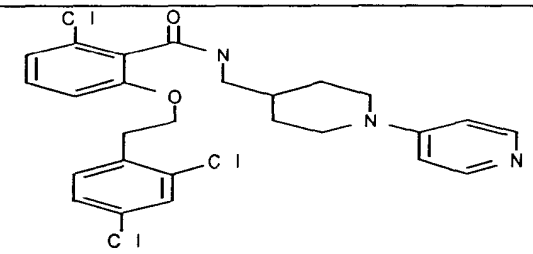
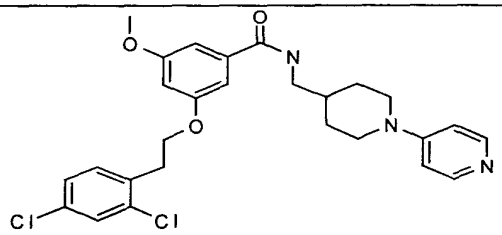
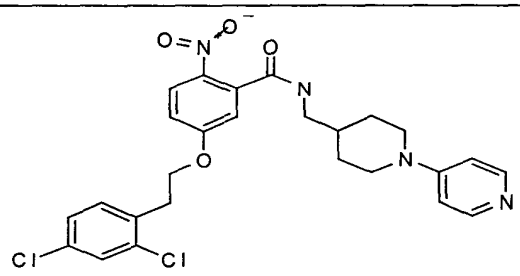
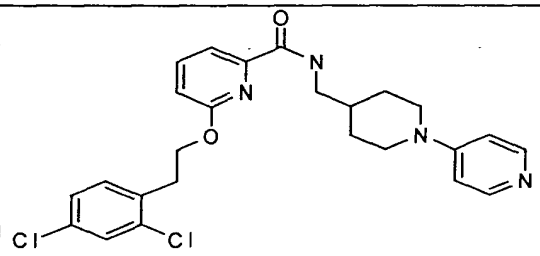
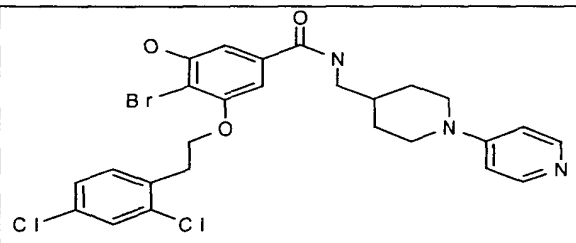
[0183] 2 g of 4-Bromo-3-[2-(2,4-dichloro-phenyl)-ethoxy]-benzoic acid methyl ester was dissolved in 10 ml of MeOH: water/3:1. 230 mg of lithium hydroxide monohydrate were added to the solution, and the reaction was stirred at RT for 16 h then at 50°C for 2 h. The solution was cooled to RT, then acidified with half-concentrated hydrochloric acid. The suspension was concentrated under reduced pressure and then extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure to yield a white solid. Yield 2.2g

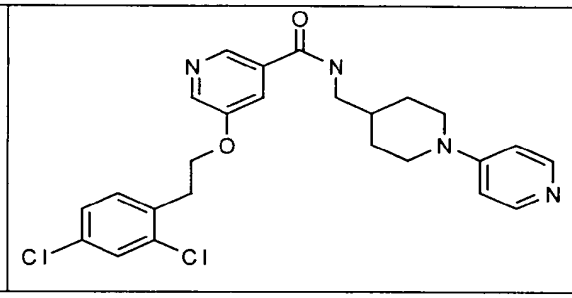
(vi) 4-Bromo-3-[2-(2,4-dichloro-phenyl)-ethoxy]-N-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-benzamide

[0184] To a solution of 200 mg 4-Bromo-3-[2-(2,4-dichloro-phenyl)-ethoxy]-benzoic acid in 4 ml CH_2Cl_2 259 µl N-NEM and subsequently 168 mg TOTU were added. After stirring for 1 h at RT 272 mg C-(3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-yl)-methylamine tris trifluoroacetate in 1 ml CH_2Cl_2 were added and the mixture was stirred for additional 2 h followed by removal of the solvent under reduced pressure. The residue was taken up in 3 ml saturated $NaHCO_3$ solution and filtered through a chem elut® cartridge by elution with ethyl acetate. After concentration under reduced pressure and purification by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.5% TFA) the fractions containing the product were evaporated and lyophilized.
Yield: 178 mg MS (ESI+): 563, chloro pattern

[0185] Analogously to example 77 the following compounds were prepared by a similar procedure:

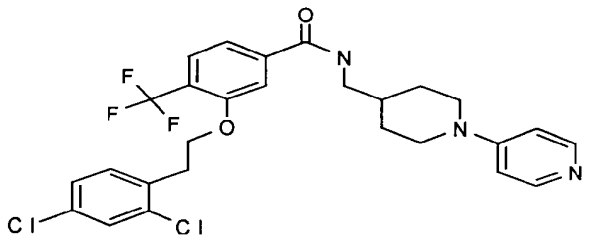
Example	Structure	MS (ESI+)
78		498, chloro pattern
79		499, chloro pattern
80		502, chloro pattern

81		518, chloro pattern
82		518, chloro pattern
83		514, chloro pattern
84		529, chloro pattern
85		485, chloro pattern
86		579, chloro pattern

87		485, chloro pattern

Example 88: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-N-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4- ylmethyl)-4-trifluoromethyl-benzamide

[0186]



(i) 3-Hydroxy-4-iodo-benzoic acid

[0187] To a solution of 26 g 3-Hydroxybenzoic acid and 43 g Na_2CO_3 in 45 mg H_2O at 100°C was added dropwise a solution of 48 g KI and 48 g iodine in 135 ml H_2O. After heating for additional 3 h the mixture was cooled to RT and acidified with concentrated HCl. The title compound precipitated as a white solid and was collected by filtration. Yield 20 g

(ii) 3-Hydroxy-4-iodo-benzoic acid methyl ester

[0188] 5 ml of thionyl chloride was added to 120 ml of MeOH at 0 °C. The solution was stirred for 10 min and 20 g of 4-Iodo-3-hydroxy-benzoic acid were added. The reaction was stirred for 16 h at RT then heated to 50 °C for 3 h. The solvents were removed under reduced pressure. The residue was used directly in the next step. Yield 21 g

(iii)4-Iodo-3-[2-(2,4-dichloro-phenyl)-ethoxy]-benzoic acid methyl ester

[0189] 6.6 g of triphenylphosphine and 5 g of 4-Iodo-3-hydroxy-benzoic acid methyl ester were dissolved in 65 ml of anhydrous THF. The solution was cooled to 0 °C to 10 °C and a solution of 3.7 ml DEAD in 7.5 ml anhydrous THF was added dropwise over 20 min. The reaction was warmed to RT and stirred for 45 min. A solution of 2.8 ml 2-(2,4-Dichlorophenyl)-ethanol in 3 ml anhydrous THF was added with cooling. The reaction was stirred at RT for 3 h, then the solvents were removed under reduced pressure. The residue was treated with n-heptane:ethyl acetate/1:1. The filtrate was dried under reduced pressure. The product was purified by silica gel chromatography, eluting with n-heptane:ethyl acetate/4:1 to n-heptane:ethyl acetate/1:1. Yield 8 g.

(iv) 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-trifluoromethyl-benzoic acid methyl ester

[0190] To suspension of 800 mg 4-Iodo-3-[2-(2,4-dichloro-phenyl)-ethoxy]-benzoic acid methyl ester, 520 mg CuI and 160 mg KF in 5 ml DMF 0.57 ml chloro-difluoro-acetic acid methyl ester were added dropwise at 120 °C and then stirred over night. After addition of 5 ml sat. aqueous NH_4Cl the suspension was filtered through a chem elut® cartridge by elution with ethyl acetate. After concentration under reduced pressure and purification by preparative HPLC (C_{18} reverse phase column, elution with a H_2O/MeCN gradient with 0.5% TFA) the fractions containing the product were evaporated and lyophilized.

Yield: 720 mg MS (ESI+): 451, chloro pattern

(v) 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-trifluoromethyl-benzoic acid

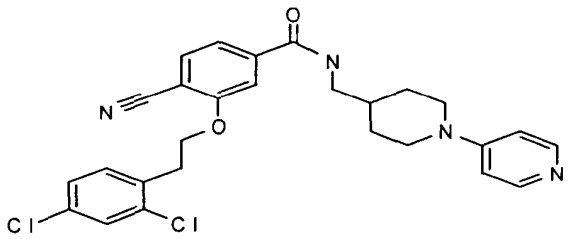
[0191] 500 mg of 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-trifluoromethyl-benzoic acid methyl ester were dissolved in 10 ml of MeOH:water/3:1. 230 mg of lithium hydroxide monohydrate were added to the solution, and the reaction was stirred at RT for 16 h then at 50 °C for 2 h. The solution was cooled to RT, then acidified with half-concentrated hydrochloric acid. The solution was concentrated under reduced pressure and then extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure to yield a white solid. Yield: 480 mg

(vi) 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-N-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-4-trifluoromethyl-benzamide

[0192] To a solution of 200 mg 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-trifluoromethyl-benzoic acid in 4 ml CH_2Cl_2 1 ml N-NEM were added followed by 237 mg TOTU. After stirring for 1 h at RT 282 mg C-(3,4,5,6-Tetrahydro-2H-[1,4'] bipyridinyl-4-yl)-methylamine tris trifluoroacetate in 1 ml CH_2Cl_2 was added and the mixture was stirred for additional 2 h followed by removal of the solvent under reduced pressure. The residue was taken up in 3 ml sat. $NaHCO_3$ solution and filtered through a chem elut® cartridge by elution with ethyl acetate. After concentration under reduced pressure and purification by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.5% TFA) the fractions containing the product were evaporated and lyophilized.
Yield: 180 mg MS (ESI+): 552, chloro pattern

Example 89: 4-Cyano-3-[2-(2,4-dichloro-phenyl)-ethoxy]-N-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl- 4-ylmethyl)-benzamide

[0193]



(i) 4-Cyano-3-[2-(2,4-dichloro-phenyl)-ethoxy]-benzoic acid methyl ester

[0194] A suspension of 800 mg 4-Iodo-3-[2-(2,4-dichloro-phenyl)-ethoxy]-benzoic acid methyl ester, 180 mg CuCN, 312 mg Et4NCN in 8 ml dioxane were purged with argon for 10 min. Then 91 mg $Pd_2(dba)_3$ and 111 mg dppf were added and the mixture refluxed overnight. After addition of 5 ml sat. aqueous NH_4Cl the suspension was filtered through a chem elut® cartridge by elution with ethyl acetate. After concentration under reduced pressure and purification by preparative HPLC (C_{18} reverse phase column, elution with a H_2O/MeCN gradient with 0.5 % TFA) the fractions containing the product were evaporated and lyophilized. Yield: 500 mg MS (ESI+): 350, chloro pattern

(ii) 4-Cyano-3-[2-(2,4-dichloro-phenyl)-ethoxy]-benzoic acid

[0195] 500mg of 4-Cyano-3-[2-(2,4-dichloro-phenyl)-ethoxy]-benzoic acid methyl ester were dissolved in 50ml of MeOH:water/3:1. 1 g of lithium hydroxide monohydrate was added to the added to the solution, and the reaction was stirred at RT for 16 h and 2 h at 50°C. The solution was cooled to RT, then acidified with half-concentrated hydrochloric acid. The suspension was concentrated under reduced pressure and then extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure to yield a white solid. Yield: 480 mg

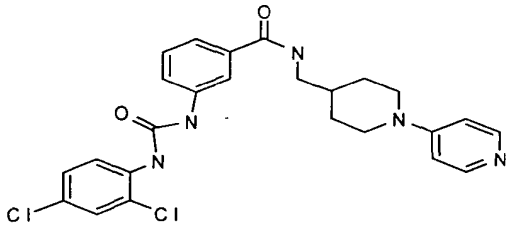
(iii) 4-Cyano-3-[2-(2,4-dichloro-phenyl)-ethoxy]-N-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-benzamide

[0196] To a solution of 200 mg 4-Cyano-3-[2-(2,4-dichloro-phenyl)-ethoxy]-benzoic acid in 4ml CH_2Cl_2 1 ml N-NEM were added followed by 237 mg TOTU. After stirring for 1 h at RT 282 mg C-(3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-

4-yl)-methylamine tris trifluoroacetate in 1 ml CH_2Cl_2 were added and the mixture was stirred for additional 2 h followed by removal of the solvent under reduced pressure. The residue was taken up in 3 ml sat. $NaHCO_3$ solution and filtered through a chem elut® cartridge by elution with ethyl acetate. After concentration under reduced pressure and purification by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.5% TFA) the fractions containing the product were evaporated and lyophilized.
Yield: 124 mg MS (ESI+): 509, chloro pattern

Example 90: 3-[3-(2,4-Dichloro-phenyl)-ureido]-N-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4- ylmethyl)-benzamide

[0197]



(i) 3-[3-(2,4-Dichloro-phenyl)-ureido]-benzoic acid

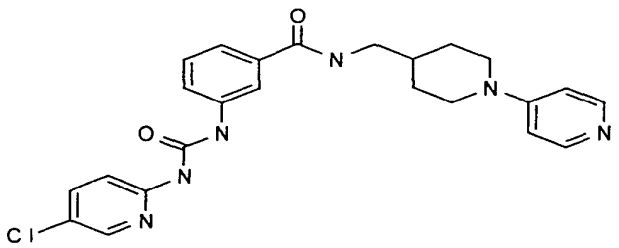
[0198] To a solution of 200 mg 3-Isocyanato-benzoic acid methyl ester in 2 ml ethyl acetate is added dropwise a solution of 162 mg 2,4-dichloroaniline in 1 ml ethyl acetate. After 5 h at RT the solvent was removed under reduced pressure and the residue dissolved in 5 ml MeOH/THF/H20 2:2:1. 100 mg lithium hydroxide monohydrate were added and the mixture stirred over night at RT. After removal of the solvent the residue was acidified by addidion of 5 ml half concentrated HCl. The precipitating acid was filtered off and dried.

(ii) 3-[3-(2,4-Dichloro-phenyl)-ureido]-N-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-benzamide

[0199] To a solution of 100 mg 3-[3-(2,4-Dichloro-phenyl)-ureido]-benzoic acid in 5 ml ethyl acetate 0.5 ml NEt_3 and 102 mg BOP-Cl were added. After 10 min 100 mg C-(3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-yl)-methylamine tris trifluoroacetate in 1 ml CH_2Cl_2 were added and the mixture stirred for 2 h at RT followed by removal of the solvent under reduced pressure. The residue was taken-up in 3 ml sat. $NaHCO_3$ solution and filtered through a chem elut® cartridge by elution with ethyl acetate. After concentration under reduced pressure and purification by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.5% TFA) the fractions containing the product were evaporated and lyophilized. Yield: 73mg MS (ESI+): 498, chloro pattern

Example 91: 3-[3-(5-Chloro-pyridin-2-yl)-ureido]-N-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4- ylmethyl)-benzamide

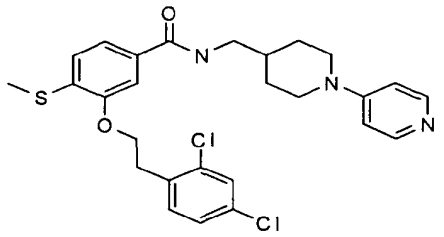
[0200]



[0201] This compound was prepared analogously to example 90 employing 5-Chloro-pyridin-2-ylamine as amine component. MS (ESI+): 465, chloro pattern

Example 92: 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methylsulfanyl-N-(3,4,5,6-tetrahydro-2H- [1,4']bipyridinyl-4-ylmethyl)-benzamide

[0202]



(i) 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methylsulfanyl-benzoic acid methyl ester

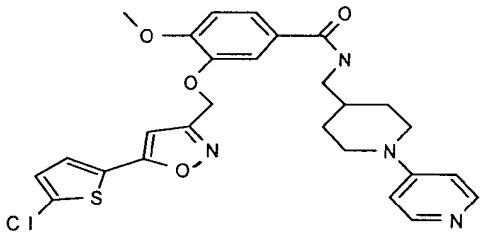
[0203] To a solution of 300 mg 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-fluoro-benzoic acid methyl esterin 0.5 ml DMSO 70 mg NaSMe were added and stirred over night. After addition of 0.3 ml H_2O and 20 mg lithium hydroxide monohydrate the solution was stirred for 5 h and the acidified with diluted HCl. The mixture was extracted with ethyl acetate, the organic layer dried over Na_2SO_4. Removal of the solvent yielded the acid as a yellow solid.

(ii) 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methylsulfanyl-N-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-benzamide

[0204] To a solution of 120 mg 3-[2-(2,4-Dichloro-phenyl)-ethoxy]-4-methylsulfanyl-benzoic acid in 5 ml ethyl acetate 0.5 ml NEt_3 and 102 mg BOP-Cl were added. After 10 min 100 mg C-(3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-yl)-methylamine tris trifluoroacetate in 1 ml CH_2Cl_2 were added and the mixture stirred for 10 h at RT followed by removal of the solvent under reduced pressure. The residue was taken up in 3 ml sat. $NaHCO_3$ solution and filtered through a chem elut® cartridge by elution with ethyl acetate. After concentration under reduced pressure and purification by preparative HPLC (C_{18} reverse phase column, elution with a H_2O/MeCN gradient with 0.5 % TFA) the fractions containing the product were evaporated and lyophilized.
Yield: 57mg MS (ESI+): 530, chloro pattern

Example 93: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethoxy]-4-methoxy-N-(3,4,5,6-tetrahydro- 2H-[1,4'] bipyridinyl-4-ylmethyl)-benzamide

[0205]



(i) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethoxy]-4-methoxy-benzoic acid

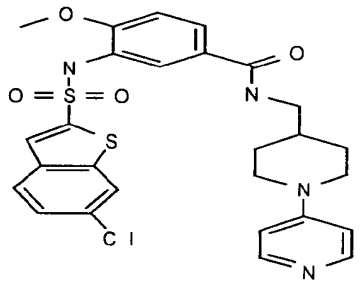
[0206] To a solution of 145 mg 3-Hydroxy-4-methoxy-benzoic acid methyl ester in 2 ml DMF 200 mg 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole [prepared as described in example 30] and 325 mg Cs_2CO_3 were added. The mixture was stirred for 3 h at RT and then diluted with 1 ml H_2O and 1 ml EtOH. After addition of 500 mg lithium hydroxide monohydrate the suspension was stirred over night. Subsequent removal of the solvent under reduced pressure and addition of diluted HCl yielded the acid as a white precipitate which was collected by filtration.

(ii) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethoxy]-4-methoxy-N-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-benzamide

[0207] To a solution of 180 mg 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethoxy]-4-methoxybenzoic acid in 5 ml ethyl acetate 0.5 ml NEt_3 and 250 mg BOP-Cl were added. After 30 min 200 mg C-(3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-yl)-methylamine tris trifluoroacetate in 1ml CH_2Cl_2 were added and the mixture stirred for 10 h at RT followed by removal of the solvent under reduced pressure. The residue was taken up in 3 ml sat. $NaHCO_3$ solution and filtered through a chem elut® cartridge by elution with ethyl acetate. After concentration under reduced pressure and purification by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.5% TFA) the fractions containing the product were evaporated and lyophilized.
Yield: 157 mg MS (ESI+): 539, chloro pattern

Example 94: 3-(6-Chloro-benzo[b]thiophene-2-sulfonylamino)-4-methoxy-N-(3,4,5,6-tetrahydro-2H- [1,4']bipyridinyl-4-ylmethyl)-benzamide

[0208]



(i) 3-(6-Chloro-benzo[b]thiophene-2-sulfonylamino)-4-methoxy-benzoic acid

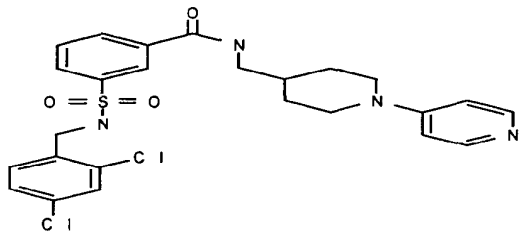
[0209] To a solution of 36 mg 3-Amino-4-methoxy-benzoic acid methyl esterin 1 ml acetonitrile and 0.1 ml NEt_3 50 mg 6-Chloro-benzo[b]thiophene-2-sulfonyl chloride [prepared by a procedure described by Ewing, William R.; Becker, Michael R.; Choi-Sledeski, Yong Mi; Pauls, Heinz W.; He, Wei; Condon, Stephen M.; Davis, Roderick S.; Hanney, Barbara A.; Spada, Alfred P.; Burns, Christopher J.; Jiang, John Z.; Li, Aiwen; Myers, Michael R.; Lau, Wan F.; Poli, Gregory B., WO99/37304] were added at RT. The mixture was stirred at RT for 5 h, then diluted with 2 ml MeOH/THF/H_2O 2:2:1. After addition of 100 mg lithium hydroxide monohydrate the suspension was stirred over night. Subsequent removal of the solvent and addition of diluted HCl yielded the acid as a white precipitate which was filtered off.

(ii) 3-(6-Chloro-benzo[b]thiophene-2-sulfonylamino)-4-methoxy-N-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-benzamide

[0210] To a solution of 80 mg 3-(6-Chloro-benzo[b]thiophene-2-sulfonylamino)-4-methoxybenzoic acid in 5 ml ethyl acetate 0.1 ml NEt_3 and 100 mg BOP-Cl were added. After 30 min 200 mg C-(3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-yl)-methylamine tris trifluoroacetate in 1 ml CH_2Cl_2 were added and the mixture stirred for 10 h at RT followed by removal of the solvent under reduced pressure. The residue was taken up in 3 ml saturated $NaHCO_3$ solution and filtered through a chem elut® cartridge by elution with ethyl acetate. After concentration under reduced pressure and purification by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.5% TFA) the fractions containing the product were evaporated and lyophilized.
Yield: 44mg MS (ESI+): 571, chloro pattern

Example 95: 3-(2,4-Dichloro-benzylsulfamoyl)-N-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4- ylmethyl)-benzamide

[0211]



(i) 3-(2,4-Dichloro-benzylsulfamoyl)-benzoic acid

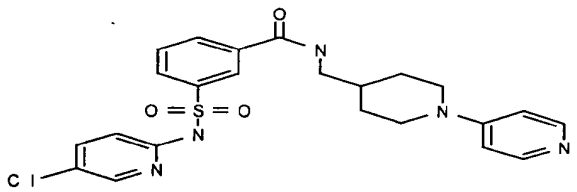
[0212] To a solution of 1.3 g 2,4-Dichloro-benzylamine and 5 mg DMAP in 10 ml pyridine 1 g 3-Chlorosulfonyl-benzoic acid in 10 ml ethyl acetate was added dropwise. After stirring over night the solvent was removed under reduced pressure and the residue was taken up in 10 ml diluted HCl and extracted with ethyl acetate. The organic layer is dried over Na_2SO_4 and concentrated to yield the acid as a yellow solid.

(ii) 3-(2,4-Dichloro-benzylsulfamoyl)-N-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-benzamide

[0213] To a solution of 100mg 3-(2,4-Dichloro-benzylsulfamoyl)-benzoic acid in 4 ml CH_2Cl_2 259 µl N-NEM and subsequently 47 mg TOTU were added. After stirring for 1 h at RT 172 mg C-(3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-yl)-methylamine tris trifluoro-acetate in 1 ml CH_2Cl_2 were added and the mixture was stirred for additional 2 h followed by removal of the solvent under reduced pressure. The residue was taken up in 3 ml saturated $NaHCO_3$ solution and filtered through a chem elut® cartridge by elution with ethyl acetate. After concentration under reduced pressure and purification by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.5% TFA) the fractions containing the product were evaporated and lyophilized.
Yield: 32 mg MS (ESI+): 533, chloro pattern

Example 96: 3-(5-Chloro-pyridin-2-ylsulfamoyl)-N-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4- ylmethyl)-benzamide

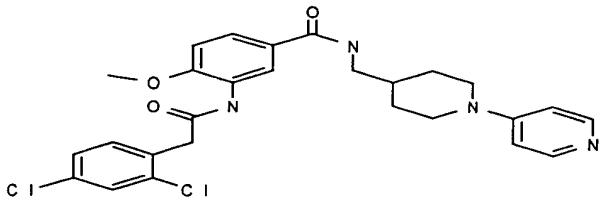
[0214]



[0215] This compound was prepared analogously to example 95 employing 5-Chloro-pyridin-2-ylamineas amine component. MS (ESI+): 486, chloro pattern

Example 97: 3-[2-(2,4-Dichloro-phenyl)-acetylamino]-4-methoxy-N-(3,4,5,6-tetrahydro-2H- [1,4']bipyridinyl-4-ylmethyl)-benzamide

[0216]



(i) 3-[2-(2,4-Dichloro-phenyl)-acetylamino]-4-methoxy-benzoic acid methyl ester

[0217] To a solution of 1.1 g 3-Amino-4-methoxy-benzoic acid methyl ester and 1g (2,4-Dichloro-phenyl)-acetic acid in 15 ml CH_2Cl_2, 2.7 ml NEt_3 and 1.24 g BOP-Cl and 10 mg DMAP were added. After stirring over night the solvent was removed under reduced pressure and the residue directly purified by chromatograpy on silica with ethyl acetate/heptane 1:5 → 1:1 to yield the ester as a yellow oil

(ii) 3-[2-(2,4-Dichloro-phenyl)-acetylamino]-4-methoxy-benzoic acid

[0218] To a solution of 400 mg 3-[2-(2,4-Dichloro-phenyl)-acetylamino]-4-methoxy-benzoic acid methyl ester in 5 ml MeOH/H_2O 2:1 56 mg lithium hydoxide monohydrate were added and the mixture was stirred over night. The suspension was diluted with 5 ml concentrated HCl to precipitate the acid. After filtration the filter cake was washed twice with water and then dried to yield the acid as a white powder.

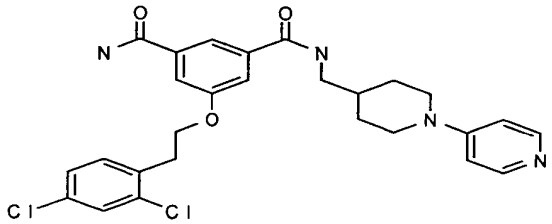
(iii) 3-[2-(2,4-Dichloro-phenyl)-acetylamino]-4-methoxy-N-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-benzamide

[0219] To a solution of 150 mg 3-[2-(2,4-Dichloro-phenyl)-acetylamino]-4-methoxy-benzoic acid in 4 ml CH_2Cl_2 259 µl N-NEM and subsequently 70 mg TOTU were added. After stirring for 1 h at RT 268 mg C-(3,4,5,6-Tetrahydro-2H-[1,4'] bipyridinyl-4-yl)-methylamine tris trifluoroacetate in 1 ml CH_2Cl_2 were added and the mixture was stirred for additional 2 h followed by removal of the solvent under reduced pressure. The residue was taken up in 3 ml sat. $NaHCO_3$ solution and filtered through a chem elut® cartridge by elution with ethyl acetate. After concentration under reduced pressure and purification by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.5% TFA) the fractions containing the product were evaporated and lyophilized. Yield: 97 mg

MS (ESI+): 527, chloro pattern

Example 98: 5-[2-(2,4-Dichloro-phenyl)-ethoxy]-N-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4- ylmethyl)-isophthalamide

[0220]



(i) 5-[2-(2,4-Dichloro-phenyl)-ethoxy]-isophthalic acid dimethyl ester

[0221] 1.75 g of triphenylphosphine and 1 g of 5-Hydroxy-isophthalic acid dimethyl ester were dissolved in 17ml of anhydrous THF. The solution was cooled to 0-10°C and a solution of 1 ml DEAD in 1 ml anhydrous THF was added

dropwise over 20 min. The reaction was warmed to RT and stirred for 45 min. A solution of 11.3 ml 2-(2,4-Dichlorophenyl)-ethanol in 1 ml anhydrous THF was added with cooling. The reaction was stirred at RT for 16 h, then the solvents were removed under reduced pressure. The residue was treated with n-heptane:ethyl acetate/1:1. The filtrate was dried under reduced pressure and the product was purified by silica gel chromatography, eluting with n-heptane:ethyl acetate/4:1 to n-heptane:ethyl acetate/3:1.

(ii) 5-[2-(2,4-Dichloro-phenyl)-ethoxy]-isophthalic acid

[0222] 500 mg 5-[2-(2,4-Dichloro-phenyl)-ethoxy]-isophthalic acid dimethyl ester were dissolved in 50 ml of MeOH: water/3:1. Then 1 g of lithium hydroxide monohydrate was added the solution, and the reaction was stirred at RT for 16 h and 2 h at 50°C. The solution was cooled to RT and then acidified with half-concentrated hydrochloric acid. The suspension was concentrated under reduced pressure and then extracted with ethylacetate. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure to yield a white solid.

(iii) 5-[2-(2,4-Dichloro-phenyl)-ethoxy]-isophthalamic acid

[0223] To a solution of 100 mg 5-[2-(2,4-Dichloro-phenyl)-ethoxy]-isophthalic acid in 3 ml THF 46 mg N,N-carbonyldiimidazole were added at RT. After 1 h 0.5 ml concentrated aqueous NH_3 solution were added and the reaction mixture was stirred for further 4 h. Concentration under reduced pressure and purification by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.5% TFA) the fractions containing the product were evaporated and lyophilized to yield a white solid.

(iv) 5-[2-(2,4-Dichloro-phenyl)-ethoxy]-N-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-isophthalamide

[0224] To a solution of 40 mg 5-[2-(2,4-Dichloro-phenyl)-ethoxy]-isophthalamic acid in 2 ml CH_2Cl_2 59 µl N-NEM and subsequently 37mg TOTU were added. After stirring for 1 h at RT 43 mg C-(3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-yl)-methylamine tris trifluoroacetate in 1 ml CH_2Cl_2 were added and the mixture was stirred for additional 2 h followed by removal of the solvent under reduced pressure. The residue was taken up in 3 ml sat. $NaHCO_3$ solution and filtered through a chem elut® cartridge by elution with ethyl acetate. After concentration under reduced pressure and purification by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.5% TFA) the fractions containing the product were evaporated and lyophilized.
Yield: 12mg MS (ESI+): 527, chloro pattern

Pharmacological testing

[0225] The ability of the compounds of the formula I to inhibit factor Xa or factor VIIa or other enzymes like thrombin, plasmin, or trypsin can be assessed by determining the concentration of the compound of the formula I that inhibits enzyme activity by 50 %, i. e. the IC_{50} value, which is related to the inhibition constant Ki. Purified enzymes are used in chromogenic assays. The concentration of inhibitor that causes a 50 % decrease in the rate of substrate hydrolysis is determined by linear regression after plotting the relative rates of hydrolysis (compared to the uninhibited control) versus the log of the concentration of the compound of formula I. For calculating the inhibition constant Ki, the IC_{50} value is corrected for competition with substrate using the formula

$$Ki = IC_{50} / \{1 + (\text{substrate concentration} / Km)\}$$

wherein Km is the Michaelis-Menten constant (Chen and Prusoff, Biochem. Pharmacol. 22 (1973), 3099-3108; I. H. Segal, Enzyme Kinetics, 1975, John Wiley & Sons, New York, 100-125; which are incorporated herein by reference).

a) Factor Xa Assay

[0226] In the assay for determining the inhibition of factor Xa activity TBS-PEG buffer (50 mM Tris-HCl, pH 7.8, 200 mM NaCl, 0.05 % (w/v) PEG-8000, 0.02 % (w/v) NaN_3) was used. The IC_{50} was determined by combining in appropriate wells of a Costar half-area microtiter plate 25 µl human factor Xa (Enzyme Research Laboratories, Inc.; South Bend, Indiana) in TBS-PEG; 40 µl 10 % (v/v) DMSO in TBS-PEG (uninhibited control) or various concentrations of the compound to be tested diluted in 10 % (v/v) DMSO in TBS-PEG; and substrate S-2765 (N(α)-benzyloxycarbonyl-D-Arg-Gly-L-Arg-p-nitroanilide; Kabi Pharmacia, Inc.; Franklin, Ohio) in TBS-PEG.
The assay was performed by pre-incubating the compound of formula I plus enzyme for 10 min. Then the assay was initiated by adding substrate to obtain a final volume of 100 µl. The initial velocity of chromogenic substrate hydrolysis was measured by the change in absorbance at 405 nm using a Bio-tek Instruments kinetic plate reader (Ceres UV900HDi) at 25 °C during the linear portion of the time course (usually 1.5 min after addition of substrate). The enzyme

concentration was 0.5 nM and substrate concentration was 140 μM.

b) Factor VIIa Assay

[0227] The inhibitory activity towards factor VIIa/tissue factor activity was determined using a chromogenic assay essentially as described previously (J. A. Ostrem et al., Biochemistry 37 (1998) 1053-1059 which is incorporated herein by reference). Kinetic assays were conducted at 25 °C in half-area microtiter plates (Costar Corp., Cambridge, Massachusetts) using a kinetic plate reader (Molecular Devices Spectramax 250). A typical assay consisted of 25 μl human factor VIIa and TF (5 nM and 10 nM, respective final concentration) combined with 40 μl of inhibitor dilutions in 10% DMSO/TBS-PEG buffer (50 mM Tris, 15 mM NaCl, 5 mM $CaCl_2$, 0.05 % PEG 8000, pH 8.15). Following a 15 minute preincubation period, the assay was initiated by the addition of 35 μl of the chromogenic substrate S-2288 (D-Ile-Pro-Arg-p-nitroanilide, Pharmacia Hepar Inc., 500 μM final concentration). The results (inhibition constants Ki (FXa) for inhibition of factor Xa) are shown in Table 1.

Table 1:

Example	KI(FXa) [μM]	Example	KI(FXa) [μM]	Example	Ki(FXa) [μM]
1	0.600	24	1.128	85	0.304
2	1.540	28	0.960	86	0.026
3	5.410	31	9.340	87	0.070
4	0.298	32	0.970	88	0.140
5	0.167	54	6.515	89	0.044
6	0.050	55	0.650	91	1.393
7	2.820	56	4.327	92	0.028
8	0.106	57	6.217	93	0.188
9	0.306	60	1.051	94	3.497
10	0.061	61	0.057	96	3.709
11	1.378	66	1.484	97	0.298
12	3.005	67	0.018	98	0.057
13	1.412	68	3.040		
14	2.184	77	0.076		
15	2.221	78	0.037		
16	4.219	79	0.029		
17	0.407	80	0.050		
18	6.200	81	0.241		
19	0.095	83	0.125		
20	0.020	84	4.883		

Claims

1. A compound of the formula I,

$$R^0\text{-}Q\text{-}X\text{-}Q'\text{-}W\text{-}U\text{-}V\text{-}G\text{-}M \quad (I)$$

wherein

R^0 is 1. a monocyclic or bicyclic 5- to 14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2, or

2. a monocyclic or bicyclic 5- to 14-membered heteroaryl, containing zero, one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2,

R^2 is halogen, $-NO_2$, -CN, $-C(O)-NH_2$, -OH, $-NH_2$, $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue, or $-(C_1-C_8)$-alkyloxy, wherein alkyloxy is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,

Q and Q' are independently of one another identical or different and are a direct bond, -C(O)-; -O-, -S-, $-NR^{10}$-, $-C(O)-NR^{10}$-, $-NR^{10}-C(O)$-, -S(O)-, $-SO_2$-, $-NR^{10}-SO_2$-, $-SO_2-NR^{10}$-, $-(C_1-C_6)$-alkylen, wherein alkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2 or -OH; or $-(C_3-C_6)$-cycloalkylen, wherein cycloalkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, $-NH_2$ or -OH;

X is a direct bond, a 3- to 7-membered heteroaryl, $-(C_1-C_6)$-alkylen, wherein alkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, $-NH_2$ or -OH; or-(C_3-C_6)-cycloalkylen, wherein cycloalkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, $-NH_2$ or -OH;

provided that when Q or Q' is $-(C_1-C_6)$-alkylen then X is -O-, -S-, $-NR^{10}$-, -C(O)-, $-C(O)-NR^{10}$-, $-NR^{10}-C(O)$-, -S(O)-, $-SO_2$-, $-NR^{10}-SO_2$- or $-SO_2-NR^{10}$-; with the proviso that if X is a direct bond, the fragment -Q -X- Q'- is not O-O, O-S, S-O, S-S, SO_2-SO_2, SO-SO, $SO-SO_2$, SO_2-SO, SO_2-S, $S-SO_2$, SO-S, S-SO; with the proviso that if X is oxygen atom or sulfur atom, then Q and Q' are not oxygen atom or sulfur atom; and with the further proviso that if X is S(O) or SO_2, then Q and Q' are not oxygen atom or sulfur atom;

W is 1. a 5- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1, 2. a 5- to14-membered heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1, 3. a 4-to 15 membered mono- or polycyclic group, wherein said mono- or polycyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1, or 4. a 4-to 15 membered mono- or polycyclic group, containing one, two, three or four heteroatoms, such as nitrogen, sulfur or oxygen, wherein said mono- or polycyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

provided that if W is a six membered aryl or heteroaryl group, then Q' and U are not in an ortho position with respect to each other;

R^1 is

1. halogen,
2. $-NO_2$,
3. -CN,
4. $-NH_2$,
5. (C_1-C_8)-alkylamino-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
6. -OH,
7. $-SO_2-NH_2$,
8. (C_1-C_8)-alkyloxy-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
9. (C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
10. (C_1-C_8)-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
11. hydroxycarbonyl-(C_1-C_8)-alkylureido-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
12. (C_1-C_8)-alkyloxycarbonyl-(C_1-C_8)-alkylureido-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
13. (C_1-C_8)-alkylsulfonyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
14. bis[(C_1-C_8)-alkyl]amino, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
15. $-C(O)-NH_2$,

16. -COOH;
17. -C(O)-(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
18. -C(O)-O-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
19. -C(O)-$NR^{11}R^{12}$,
20. -C(O)-NH-(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
21. -C(O)-NH-[(C_1-C_8)-alkyl]$_2$, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
22. -C(NH)-NH_2,
23. ureido,
24. -(C_1-C_8)-alkylthio, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, or
25. $R^{11}R^{12}N$-, or

two R^1 residues bonded to adjacent ring carbon atoms together with the carbon atoms to which they are bonded form an aromatic ring condensed to W, where the ring formed by the two R^1 residues is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

R^{11} and R^{12} together with the nitrogen atom to which they are bonded form a saturated or unsaturated 5- to 6-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^{11} and R^{12} can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen, and in which one or two of the ring carbon atoms can be substituted by oxo to form -C(O) - residue(s),

R^{13} is halogen, $-NO_2$, -CN, -OH, -(C_1-C_8)-alkyl, -(C_1-C_8)-alkyloxy, $-CF_3$, $-C(O)-NH_2$ or $-NH_2$,

R^{10} is hydrogen atom or -(C_1-C_4)-alkyl,

U and G are independently of one another identical or different and are a direct bond, $-(CH_2)_m$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n$, $-(CH_2)-SO_2-(CH_2)_n-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n$,$-(CH_2)_m-C(O)-(CH_2)_n$, $-(CH_2)-S-(CH_2)_n$,$-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n$, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n$, $-(CH_2)_m-CH(OH)-(CH_2)_n$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n$ or $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n$,

n and m are are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6, wherein the alkylen residues are unsubstituted or mono-, di- or trisubstituted independently of one another by -(C_1-C_4)-alkyl; -C(O)-OH, -C(O)-O-(C_1-C_4)-alkyl, $-C(O)-NR^4R^5$, $-SO_2$, $-NR^4R^5$ or -(C_1-C_8)-alkylsulfonyl,

R^4 and R^5 are independently of one another identical or different and are hydrogen atom, -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -(C_6-C_{14})-aryl-(C_1-C_4)-alkyl-, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, -(C_6-C_{14})-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -(C_6-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} or -(C_6-C_{14})-heteroaryl-(C_1-C_4)-alkyl-, wherein alkyl and heteroaryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, or

R^4 and R^5 together with the nitrogen atom to which they are bonded form a saturated 5 - to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^4 and R^5 can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

V is
1. a direct bond,
2. -(C_1-C_6)-alkylen, which is branched or unbranched and which is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, =O, -CN, -OH, $-NR^4R^5$, -C(O) -OH, -C(O)-O-(C_1-C_4)-alkyl, $-SO_2-NR^4R^5$, $-C(O)-NR^4R^5$ or -(C_1-C_8)-alkylsulfonyl,
3. a 3- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
4. a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
5. a heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted inde-

pendently of one another by R^{14},

R^{14} is halogen, -OH, $-NR^4R^5$, =O, $-(C_1-C_4)$-alkyl, $-(C_1-C_4)$-alkoxy, $-NO_2$, -C(O)-OH, -CN, $-C(O)-O-(C_1-C_4)$-alkyl, $-C(O)-NR^4R^5$, $-(C_1-C_8)$-alkylsulfonyl, $-C(O)-NR^4R^5$, $-SO_2$, $-C(O)-NH-(C_1-C_8)$-alkyl, $-C(O)-NH-[(C_1-C_8)\text{-alkyl}]_2$, $-NR^{10}-C(O)-NH-(C_1-C_8)$-alkyl, $-C(O)-NH_2$, $-SO_2-NR^4R^5$, $-SR^4$, or $-NR^{10}-C(O)-NH-[(C_1-C_8)\text{-alkyl}]_2$, wherein R^4, R^5 and R^{10} are as defined above, and

M is
1. a hydrogen atom,
2. $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
3. $-C(O)-NR^4R^5$,
4. $-(C_6-C_{14})$-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
5. $-(C_6-C_{14})$-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
6. a 3- to 7-membered cyclic group, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
7. a 3- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, wherein R^{14} is defined above,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

2. A compound of formula I as claimed in claim 1, wherein

R^0 is phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2,

pyridyl, wherein pyridyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2,
pyrimidyl, wherein pyrimidyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2, or
naphthyl, wherein naphthyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2,

R^2 is as defined above and wherein the alkyl- or alkyloxy residue is unsubstituted or mono-, di- or trisubstituted independently of one another by an amino residue or a methoxy residue,

Q and Q' are as defined above and wherein the alkylen- or cycloalkylen residue is unsubstituted or mono-, di- or trisubstituted independently of one another by $-NH_2$ or -OH;

X is is as defined above,

W is phenyl, pyridyl, pyrimidyl, benzoxazole, benzthiazole, indole, benzo[1,3]dioxole, or naphthyl, wherein W is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

provided that if W is a six membered aryl or heteroaryl group, Q' and U are not in an ortho position with respect to each other; R^1, R^{10}, R^{11}, R^{12} and R^{13} are as defined above,

U and G are independently of one another identical or different and are a direct bond,
$-(CH_2)_m$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n$, $-(CH_2)_m-C(O)-(CH_2)_n$, $-(CH_2)-S-(CH_2)_n$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n$, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n$ or $-(CH_2)_m-CH(OH)-(CH_2)_n$,
wherein n, m, R^4 and R^5 are as defined in claim 1, V and M are as defined in claim 1.

3. A compound of formula I as claimed in claim 1 or 2, wherein

R^0 is phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2,
pyridyl, wherein pyridyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2,
pyrimidyl, wherein pyrimidyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2, or

naphthyl, wherein naphthyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2,

R^2 is halogen, -CN, $-NH_2$, $-C(O)-NH_2$, $-(C_1-C_4)$-alkyl, or $-(C_1-C_4)$-alkyloxy, wherein the alkyl- or alkyloxy residue is unsubstituted or mono-, di- or trisubstituted independently of one another by an amino residue or a methoxy residue,

Q and Q' are independently of one another identical or different and are a direct bond, -C(O)-; -O-, $-NR^{10}-$, $-C(O)-NR^{10}-$, $-NR^{10}-C(O)-$, $-SO_2-$, $-NR^{10}-SO_2-$, $-SO_2-NR^{10}-$, $-(C_1-C_4)$-alkylen, wherein alkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen; or $-(C_3-C_6)$-cycloalkylen, wherein cycloalkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen;

X is a direct bond, $-(C_1-C_3)$-alkylen, wherein alkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen; or
$-(C_3-C_6)$-cycloalkylen, wherein cycloalkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen;
provided that when Q or Q' is $-(C_1-C_3)$-alkylen then X is -O-, $-NR^{10}-$, -C(O)-, $-C(O)-NR^{10}-$, $-NR^{10}-C(O)-$, $-SO_2-$, $-NR^{10}-SO_2-$ or $-SO_2-NR^{10}-$;

with the proviso that if X is a direct bond, the fragment -Q -X- Q'- is not O-O, SO_2-SO_2, or $SO-SO_2$; and
with the proviso that if X is oxygen atom, then Q and Q' are not oxygen atom or sulfur atom; and
with the further proviso that if X is SO_2, then Q and Q' are not oxygen atom or sulfur atom;

W is phenyl, pyridyl, pyrimidyl, benzoxazole, benzthiazole, indole, benzo[1,3]dioxole, or naphthyl, wherein W is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

provided that if W is a six membered aryl or heteroaryl group, Q' and U are not in an ortho position with respect to each other;

R^1 is
1. halogen,
2. $-NO_2$,
3. -CN,
4. $-NH_2$,
5. (C_1-C_6)-alkylamino-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
6. -OH,
7. $-SO_2-NH_2$,
8. (C_1-C_6)-alkyloxy-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
9. (C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
10 (C_1-C_6)-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
11. hydroxycarbonyl-(C_1-C_6)-alkylureido-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
12. (C_1-C_6)-alkyloxycarbonyl-(C_1-C_6)-alkylureido-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
13. (C_1-C_6)-alkylsulfonyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
14. bis[(C_1-C_6)-alkyl]amino, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
15. $-C(O)-NH_2$,
16. -C(O)-OH,
17. $-C(O)-(C_1-C_6)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
18. $-C(O)-NH-(C_1-C_6)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
19. $-C(O)-NH-[(C_1-C_6)\text{-alkyl}]_2$, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

20. -C(NH)-NH_2,
21. ureido,
22. -(C_1-C_6)-alkylthio, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, or
23. $R^{11}R^{12}N$-, or

two R^1 residues bonded to adjacent ring carbon atoms together with the carbon atoms to which they are bonded form an aromatic ring condensed to W, where the ring formed by the two R^1 residues is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

R^{11} and R^{12} together with the nitrogen atom to which they are bonded form a saturated or unsaturated 5- to 6-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^{11} and R^{12} can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen, and in which one or two of the ring carbon atoms can be substituted by oxo to form -C(O)- residue(s),

R^{13} is halogen, -CN, -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyloxy, $-CF_3$, -C(O)-NH_2 or $-NH_2$,

R^{10} is hydrogen atom or -(C_1-C_4)-alkyl,

U and G are independently of one another identical or different and are a direct bond, -$(CH_2)_m$, -$(CH_2)_m$-O-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-NR^{10} -$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$, -$(CH_2)_m$-C(O)-$(CH_2)_n$, -(CH_2)-S-$(CH_2)_n$, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$, or -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$,

n and m are are independently of one another identical or different and are the integers zero, 1, 2 or 3, wherein the alkylen residues are unsubstituted or mono-, di- or trisubstituted independently of one another by -(C_1-C_4)-alkyl; -C(O)-OH, -C(O)-O-(C_1-C_4)-alkyl, -C(O)-NR^4R^5, $-SO_2$, $-NR^4R^5$ or -(C_1-C_8)-alkylsulfonyl,

R^4 and R^5 are independently of one another identical or different and are hydrogen atom, -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -(C_6-C_{14})-aryl-(C_1-C_4)-alkyl-,

wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, -(C_6-C_{14})-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -(C_6-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} or -(C_6-C_{14})-heteroaryl-(C_1-C_4)-alkyl-, wherein alkyl and heteroaryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, or

R^4 and R^5 together with the nitrogen atom to which they are bonded form a saturated 5- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^4 and R^5 can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

V is
1. a direct bond,
2. -(C_1-C_4)-alkylen, which is branched or unbranched and which is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, =O, -CN, -OH, -NR^4R^5, -C(O)-OH, -C(O)-O-(C_1-C_4)-alkyl, $-SO_2$, -NR^4R^5, -C(O)-NR^4R^5 or -(C_1-C_8)-alkylsulfonyl,
3. a 5- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
4. a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
5. a heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

R^{14} is halogen, -OH, -NR^4R^5, =O, -(C_1-C_4)-alkyl, -(C_1-C_4)-alkoxy, $-NO_2$, -C(O)-OH, -CN, -C(O)-O-(C_1-C_4)-alkyl, -C(O)-NR^4R^5, -(C_1-C_8)-alkylsulfonyl, -C(O)-NR^4R^5, -SO_2-NR^4R^5, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH-[(C_1-C_8)-alkyl]$_2$, -NR^{10}-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH_2 or -NR^{10}-C(O)-NH-[(C_1-C_8)-alkyl]$_2$,

wherein R^4, R^5 and R^{10} are as defined above, and

M is
1. a hydrogen atom,
2. -(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

3. -C(O)-NR^4R^5,
4. -(C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
5. -(C_6-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
6. a 5- to 7-membered cyclic group, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
7. a 5- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, wherein R^{14} is defined above.

4. A compound of formula I as claimed in one or more of claims 1 to 3, wherein

R^0 is phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2, or
pyridyl, wherein pyridyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2,

R^2 is halogen, -CN, -C(O)-NH_2, -(C_1-C_4)-alkyl, or -(C_1-C_4)-alkyloxy, wherein the alkyl- or alkyloxy residue is unsubstituted or mono-, di- or trisubstituted independently of one another by an amino residue or a methoxy residue,

Q and Q' are independently of one another identical or different and are a direct bond, -C(O)-; -O-, -NR^{10}-, -C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, -NR^{10}-SO_2-, -SO_2-NR^{10}-, or -(C_1-C_4)-alkylen,

X is a direct bond or -(C_1-C_3)-alkylen,
provided that when Q or Q' is -(C_1-C_3)-alkylen then X is -O-, -NR^{10}-, -C(O)-, -C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, -NR^{10}-SO_2- or -SO_2-NR^{10}-;

with the proviso that if X is a direct bond, the fragment -Q -X- Q'- is not O-O or SO_2-SO_2;
and with the proviso that if X is oxygen atom, then Q and Q' are not oxygen atom or sulfur atom; and
with the further proviso that if X is SO_2, then Q and Q' are not oxygen atom or sulfur atom;

W is phenyl, pyridyl or pyrimidyl, wherein W is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

provided that Q' and U are not in an ortho position with respect to each other;

R^1 is
1. halogen,
2. -NO_2,
3. -CN,
4. -NH_2,
5. (C_1-C_4)-alkylamino-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
6. -OH,
7. -SO_2-NH_2,
8. (C_1-C_4)-alkyloxy-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
9. (C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
10. (C_1-C_4)-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
11. hydroxycarbonyl-(C_1-C_4)-alkylureido-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
12. (C_1-C_4)-alkyloxycarbonyl-(C_1-C_4)-alkylureido-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
13. (C_1-C_4)-alkylsulfonyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
14. bis[(C_1-C_4)-alkyl]amino, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

15. -C(O)-NH_2,
16. -C(O)-OH,
17. -C(O)-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
18. -C(O)-NH-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
19. -C(O)-NH-[(C_1-C_4)-alkyl]$_2$, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
20. -C(NH)-NH_2,
21. ureido,
22. -(C_1-C_4)-alkylthio, wherein alkylthio is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, or
23. $R^{11}R^{12}N$-, or

two R^1 residues bonded to adjacent ring carbon atoms together with the carbon atoms to which they are bonded form an aromatic ring condensed to W, where the ring formed by the two R^1 residues is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

R^{11} and R^{12} together with the nitrogen atom to which they are bonded form a saturated or unsaturated 5- to 6-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^{11} and R^{12} can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen,

R^{13} is halogen, -CN, -(C_1-C_4)-alkyl, -(C_1-C_4)-alkyloxy, -CF_3, -C(O)-NH_2 or -NH_2,

R^{10} is hydrogen atom or -(C_1-C_4)-alkyl,

U and G are independently of one another identical or different and are a direct bond, -$(CH_2)_m$, -$(CH_2)_m$-C(O)-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$, -$(CH_2)_m$-C(O)-$(CH_2)_n$, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$, or -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$,

n and m are are independently of one another identical or different and are the integers zero, 1, 2 or 3, wherein the alkylen residues are unsubstituted or mono-, di- or trisubstituted independently of one another by -(C_1-C_4)-alkyl; -C(O)-OH, -C(O)-O-(C_1-C_4)-alkyl or -C(O)-NR^4R^5,

R^4 and R^5 are independently of one another identical or different and are hydrogen atom, -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -(C_6-C_{14})-aryl-(C_1-C_4)-alkyl-, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, -(C_6-C_{14})-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -(C_6-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} or -(C_6-C_{14})-heteroaryl-(C_1-C_4)-alkyl-, wherein alkyl and heteroaryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, or

R^4 and R^5 together with the nitrogen atom to which they are bonded form a saturated 5- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^4 and R^5 can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

V is
1. a direct bond,
2. -(C_1-C_4)-alkylen, which is branched or unbranched and which is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, =O, -CN, -OH, -NR^4R^5, -C(O)-OH, -C(O)-O-(C_1-C_4)-alkyl, -SO_2-NR^4R^5, -C(O)-NR^4R^5 or -(C_1-C_4)-alkylsulfonyl,
3. a 5- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
4. a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
5. a 6- to14-membered heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

R^{14} is halogen, -OH, -NR^4R^5, =O, -(C_1-C_4)-alkyl, -(C_1-C_4)-alkoxy, -NO_2, -C(O)-OH, -CN, -C(O)-O-(C_1-C_4)-alkyl, -C(O)-NR^4R^5, -(C_1-C_8)-alkylsulfonyl, -C(O)-NR^4R^5, -SO_2-NR^4R^5, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH-[(C_1-C_8)-alkyl]$_2$, -NR^{10}-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH_2 or -NR^{10}-C(O)-NH-[(C_1-C_8)-alkyl]$_2$, wherein R^4, R^5 and R^{10} are as defined above, and

M is
1. a hydrogen atom,
2. -(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
3. -C(O)-NR^4R^5,
4. -(C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
5. -(C_6-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
6. a 5- to 7-membered cyclic group, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
7. a 5- to 7-member cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, wherein R^{14} is defined above.

5. A compound of formula I as claimed in one or more of claims 1 to 4, wherein

R^0 is phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R^2, or
pyridyl, wherein pyridyl is unsubstituted or mono-, disubstituted independently of one another by R^2,

R^2 is halogen, -CN, -C(O)-NH_2, -(C_1-C_3)-alkyl, or -(C_1-C_3)-alkyloxy, wherein the alkyl- or alkyloxy residue is unsubstituted or mono-, di- or trisubstituted independently of one another by an amino residue or a methoxy residue,

Q and Q' are independently of one another identical or different and are a direct bond, -C(O)-; -O-, -NR^{10}-, -C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, -NR^{10}-SO_2-, -SO_2-NR^{10}-, or -(C_1-C_4)-alkylen,

X is a direct bond or -(C_1-C_3)-alkylen,
provided that when Q or Q' is -(C_1-C_3)-alkylen then X is -O-, -NR^{10}-, -C(O)-, -C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, -NR^{10}-SO_2- or -SO_2-NR^{10}-;

with the proviso that if X is a direct bond, the fragment -Q -X- Q'- is not O-O or SO_2-SO_2;
and with the proviso that if X is oxygen atom, then Q and Q' are not oxygen atom or sulfur atom; and
with the further proviso that if X is SO_2, then Q and Q' are not oxygen atom or sulfur atom;

W is phenyl, pyridyl or pyrimidyl, wherein W is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

provided that Q' and U are not in an ortho position with respect to each other;

R^1 is
1. halogen,
2. -NO_2,
3. -CN,
4. -NH_2,
5. (C_1-C_4)-alkylamino-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
6. -OH,
7. -SO_2-NH_2,
8. (C_1-C_4)-alkyloxy-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
9. (C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
10. (C_1-C_4)-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
11. (C_1-C_4)-alkylsulfonyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
12. bis[(C_1-C_4)-alkyl]amino, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
13. -C(O)-NH_2,

14. -C(O)-OH,
15. -C(O)-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
16. -C(O)-NH-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
17. -C(O)-NH-[(C_1-C_4)-alkyl]$_2$, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
18. -C(NH)-NH_2,
19. ureido,
20. -(C_1-C_4)-alkylthio, wherein alkylthio is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, or
21. $R^{11}R^{12}N$-, or

two R^1 residues bonded to adjacent ring carbon atoms together with the carbon atoms to which they are bonded form an aromatic ring condensed to W, where the ring formed by the two R^1 residues is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

R^{11} and R^{12} together with the nitrogen atom to which they are bonded form a saturated or unsaturated 5- to 6-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^{11} and R^{12} can contain one or two identical or different ring heteroatoms chosen from oxygen or nitrogen,

R^{13} is halogen, -CN, -(C_1-C_4)-alkyl, -(C_1-C_4)-alkyloxy, -CF_3, -C(O)-NH_2 or -NH_2,

R^{10} is hydrogen atom or -(C_1-C_4)-alkyl,

U is a direct bond, -$(CH_2)_m$-, -$(CH_2)_m$-C(O)-NR^{10} -$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-C(O) -$(CH_2)_n$-, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$-, or -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$-,

n and m are are independently of one another identical or different and are the integers zero, 1, 2 or 3, wherein the alkylen residues are unsubstituted or mono-, di- or trisubstituted independently of one another by -(C_1-C_4)-alkyl; -C(O)-OH, -C(O)-O-(C_1-C_4)-alkyl or -C(O)-NR^4R^5,

R^4 and R^5 are independently of one another identical or different and are hydrogen atom, -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -(C_6-C_{14})-aryl-(C_1-C_4)-alkyl-, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, -(C_6-C_{14})-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -(C_6-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} or -(C_6-C_{14})-heteroaryl-(C_1-C_4)-alkyl-, wherein alkyl and heteroaryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, or

R^4 and R^5 together with the nitrogen atom to which they are bonded form a saturated 5- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^4 and R^5 can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

G is a direct bond, -$(CH_2)_m$-, -$(CH_2)_m$-O-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O) -NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-$(CH_2)_n$-, -(CH_2)-S-$(CH_2)_n$-, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$- or -$(CH_2)_m$-SO_2-$(CH_2)_n$-,
wherein n, m, and R^{10} are as defined above

V is
1. a direct bond,
2. -(C_1-C_4)-alkylen, which is branched or unbranched and which is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, =O, -CN, -NR^4R^5, -C(O)-OH, -C(O)-O-(C_1-C_4)-alkyl, -SO_2-NR^4R^5, -C(O)-NR^4R^5 or -(C_1-C_4)-alkylsulfonyl,
3. a 5- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
4. a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
5. a 6- to14-membered heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

R^{14} is halogen, -OH, -NR^4R^5, =O, -(C_1-C_4)-alkyl, -(C_1-C_4)-alkoxy, -NO_2, -C(O)-OH, -CN, -C(O)

-O-(C_1-C_4)-alkyl, -C(O)-NR^4R^5, -(C_1-C_8)-alkylsulfonyl, -C(O)-NR^4R^5, -SO_2-NR^4R^5, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH-[(C_1-C_8)-alkyl]$_2$, -NR^{10}-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH_2 or -NR^{10}-C(O)-NH-[(C_1-C_8)-alkyl]$_2$, wherein R^4, R^5 and R^{10} are as defined above, and

M is
1. a hydrogen atom,
2. -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
3. -C(O)-NR^4R^5,
4. -(C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
5. -(C_6-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
6. a 5- to 7-membered cyclic group, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
7. a 5- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, wherein R^{14} is defined above.

6. A compound of the formula I as claimed in one or more of claims 1 to 5, wherein

R^0 is phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R^2, or
pyridyl, wherein pyridyl is unsubstituted or mono-, disubstituted independently of one another by R^2,

R^2 is halogen, -CN, -C(O)-NH_2, -(C_1-C_3)-alkyl, or -(C_1-C_3)-alkyloxy, wherein the alkyl- or alkyloxy residue is unsubstituted or mono-, di- or trisubstituted independently of one another by an amino residue or a methoxy residue,

Q and Q' are independently of one another identical or different and are a direct bond, - C(O)-; -O-, -NR^{10}-, -C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, -NR^{10}-SO_2-, -SO_2-NR^{10}-, or -(C_1-C_4)-alkylen,

X is a direct bond or -(C_1-C_3)-alkylen,
provided that when Q or Q' is -(C_1-C_3)-alkylen then X is -O-, -NR^{10}-, -C(O)-, -C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, -NR^{10}-SO_2- or -SO_2-NR^{10}-;

with the proviso that if X is a direct bond, the fragment -Q -X- Q'- is not O-O or SO_2-SO_2;
and with the proviso that if X is oxygen atom, then Q and Q' are not oxygen atom or sulfur atom; and
with the further proviso that if X is SO_2, then Q and Q' are not oxygen atom or sulfur atom;

W is phenyl or pyridyl, wherein W is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

provided that Q' and U are not in an ortho position with respect to each other;

R^1 is
1. halogen,
2. -NO_2,
3. -CN,
4. -NH_2,
5. (C_1-C_4)-alkylamino-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
6. -OH,
7. -SO_2-NH_2,
8. (C_1-C_4)-alkyloxy-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
9. (C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
10. (C_1-C_4)-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
11. (C_1-C_4)-alkylsulfonyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

12. bis[(C_1-C_4)-alkyl]amino, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
13. -C(O)-NH_2,
14. -C(O)-OH,
15. -C(O)-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
16. -C(O)-NH-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
17. -C(O)-NH-[(C_1-C_4)-alkyl]$_2$, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
18. -C(NH)-NH_2,
19. ureido,
20. -(C_1-C_4)-alkylthio, wherein alkylthio is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, or
21. $R^{11}R^{12}N$-, or

two R^1 residues bonded to adjacent ring carbon atoms together with the carbon atoms to which they are bonded form an aromatic ring condensed to W, where the ring formed by the two R^1 residues is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

R^{11} and R^{12} together with the nitrogen atom to which they are bonded form a saturated or unsaturated 5- to 6-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^{11} and R^{12} can contain one or two identical or different ring heteroatoms chosen from oxygen or nitrogen,

R^{13} is halogen, -CN, -(C_1-C_4)-alkyl, -(C_1-C_4)-alkyloxy, -CF_3, -C(O)-NH_2 or -NH_2,

R^{10} is hydrogen atom or -(C_1-C_4)-alkyl,

U is a direct bond, -$(CH_2)_m$, -$(CH_2)_m$-C(O)-NR^{10} -$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$, -$(CH_2)_m$-C(O)-$(CH_2)_n$, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$, or -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$,

n and m are are independently of one another identical or different and are the integers zero, 1, 2 or 3, wherein the alkylen residues are unsubstituted or mono-, di- or trisubstituted independently of one another by -(C_1-C_4)-alkyl; -C(O)-OH, -C(O)-O-(C_1-C_4)-alkyl or -C(O)-NR^4R^5,

R^4 and R^5 are independently of one another identical or different and are hydrogen atom, -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -(C_6-C_{14})-aryl-(C_1-C_4)-alkyl-,

wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, -(C_6-C_{14})-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -(C_6-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} or -(C_6-C_{14})-heteroaryl-(C_1-C_4)-alkyl-, wherein alkyl and heteroaryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, or

R^4 and R^5 together with the nitrogen atom to which they are bonded form a saturated 5- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^4 and R^5 can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

G is a direct bond, -$(CH_2)_m$, -$(CH_2)_m$-O-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$, -$(CH_2)_m$-C(O)-$(CH_2)_n$, -(CH_2)-S-$(CH_2)_n$, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$ or -$(CH_2)_m$-SO_2-$(CH_2)_n$, wherein n, m, and R^{10} are as defined above

V is
1. a direct bond,
2. -(C_1-C_4)-alkylen, which is branched or unbranched and which is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, =O, -CN, -NR^4R^5, -C(O)-OH, -C(O)-O-(C_1-C_4)-alkyl, -SO_2-NR^4R^5, -C(O)-NR^4R^5 or -(C_1-C_4)-alkylsulfonyl,
3. a 5- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
4. a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted inde-

pendently of one another by R^{14}, or
5. a 6- to14-membered heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

R^{14} is halogen, -OH, $-NR^4R^5$, =O, $-(C_1-C_4)$-alkyl, $-(C_1-C_4)$-alkoxy, $-NO_2$, -C(O)-OH, -CN, $-C(O)-O-(C_1-C_4)$-alkyl, $-C(O)-NR^4R^5$, $-(C_1-C_8)$-alkylsulfonyl, $-C(O)-NR^4R^5$, $-SO_2-NR^4R^5$, $-C(O)-NH-(C_1-C_8)$-alkyl, $-C(O)-NH-[(C_1-C_8)-alkyl]_2$, $-NR^{10}-C(O)-NH-(C_1-C_8)$-alkyl, $-C(O)-NH_2$ or $-NR^{10}-C(O)-NH-[(C_1-C_8)-alkyl]_2$,
wherein R^4, R^5 and R^{10} are as defined above, and

M is
1. a hydrogen atom,
2. $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
3. $-C(O)-NR^4R^5$,
4. $-(C_6-C_{14})$-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
5. $-(C_6-C_{14})$-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
6. a 5- to 7-membered cyclic group, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
7. a 5- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, wherein R^{14} is defined above.

7. A compound of formula I as as claimed in one or more of claims 1 to 6, wherein

R^0 is phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R^2, or
pyridyl, wherein pyridyl is unsubstituted or mono-, disubstituted independently of one another by R^2,

R^2 is halogen, -CN, $-C(O)-NH_2$, $-(C_1-C_3)$-alkyl, or $-(C_1-C_3)$-alkyloxy, wherein the alkyl- or alkyloxy residue is unsubstituted or mono-, di- or trisubstituted independently of one another by an amino residue or a methoxy residue,

Q and Q' are independently of one another identical or different and are a direct bond, -C(O)-; -O-, $-NR^{10}$-, $-C(O)-NR^{10}$-, $-NR^{10}-C(O)$-, $-SO_2$-, $-NR^{10}-SO_2$-, $-SO_2-NR^{10}$-, or $-(C_1-C_4)$-alkylen,

X is a direct bond or $-(C_1-C_3)$-alkylen,
provided that when Q or Q' is $-(C_1-C_3)$-alkylen then X is -O-, $-NR^{10}$-, -C(O)-, $-C(O)-NR^{10}$-, $-NR^{10}-C(O)$-, $-SO_2$-, $-NR^{10}-SO_2$- or $-SO_2-NR^{10}$-;

with the proviso that if X is a direct bond, the fragment -Q -X- Q'- is not O-O or SO_2-SO_2;
and with the proviso that if X is oxygen atom, then Q and Q' are not oxygen atom or sulfur atom; and
with the further proviso that if X is SO_2, then Q and Q' are not oxygen atom or sulfur atom;

W is phenyl or pyridyl, wherein W is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

provided that Q' and U are not in an ortho position with respect to each other;

R^1 is
1. halogen,
2. $-NO_2$,
3. -CN,
4. $-NH_2$,
5. (C_1-C_4)-alkylamino-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
6. -OH,
7. $-SO_2-NH_2$,
8. (C_1-C_4)-alkyloxy-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independ-

ently of one another by R^{13},
9. $(C_6$-$C_{14})$-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
10. $(C_1$-$C_4)$-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
11. $(C_1$-$C_4)$-alkylsulfonyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
12. bis[$(C_1$-$C_4)$-alkyl]amino, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
13. -C(O)-NH_2,
14. -C(O)-OH,
15. -C(O)-$(C_1$-$C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
16. -C(O)-NH-$(C_1$-$C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
17. -C(O)-NH-[$(C_1$-$C_4)$-alkyl]$_2$, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
18. -C(NH)-NH_2,
19. ureido,
20. -$(C_1$-$C_4)$-alkylthio, wherein alkylthio is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, or
21. $R^{11}R^{12}N$-, or

two R^1 residues bonded to adjacent ring carbon atoms together with the carbon atoms to which they are bonded form an aromatic ring condensed to W, where the ring formed by the two R^1 residues is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

R^{11} and R^{12} together with the nitrogen atom to which they are bonded form a saturated or unsaturated 5- to 6-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^{11} and R^{12} can contain one or two identical or different ring heteroatoms chosen from oxygen or nitrogen,

R^{13} is halogen, -CN, -$(C_1$-$C_4)$-alkyl, -$(C_1$-$C_4)$-alkyloxy, -CF_3, -C(O)-NH_2 or -NH_2,

R^{10} is hydrogen atom or -$(C_1$-$C_4)$-alkyl,

U is -$(CH_2)_m$-C(O)-NR^{10} -$(CH_2)_n$, wherein n and m are independently of one another identical or different and are the integers zero, 1 or 2,

R^4 and R^5 are independently of one another identical or different and are hydrogen atom, -$(C_1$-$C_6)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -$(C_6$-$C_{14})$-aryl-$(C_1$-$C_4)$-alkyl-,

wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, -$(C_6$-$C_{14})$-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -$(C_6$-$C_{14})$-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} or -$(C_6$-$C_{14})$-heteroaryl-$(C_1$-$C_4)$-alkyl-, wherein alkyl and heteroaryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, or

R^4 and R^5 together with the nitrogen atom to which they are bonded form a saturated 5- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^4 and R^5 can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

G is a direct bond, -$(CH_2)_m$, -$(CH_2)_m$-O-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$,-$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$,-$(CH_2)_m$-C(O)-$(CH_2)_n$, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$, -$(CH_2)_m$-SO_2-$(CH_2)_n$ or -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$,
wherein n, m, and R^{10} are as defined above

V is
1. a 5- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
2. a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
3. a 6- to14-membered heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or

trisubstituted independently of one another by R^{14},

R^{14} is halogen, -OH, $-NR^4R^5$, =O, $-(C_1-C_4)$-alkyl, $-(C_1-C_4)$-alkoxy, $-NO_2$, -C(O)-OH, -CN, $-C(O)-O-(C_1-C_4)$-alkyl, $-C(O)-NR^4R^5$, $-(C_1-C_8)$-alkylsulfonyl, $-C(O)-NH_2$, $-SO_2-NR^4R^5$, $-C(O)-NH-(C_1-C_8)$-alkyl, $-C(O)-NH-[(C_1-C_8)\text{-alkyl}]_2$, $-NR^{10}-C(O)-NH-(C_1-C_8)$-alkyl, $-C(O)-NH_2$ or $-NR^{10}-C(O)-NH-[(C_1-C_8)\text{-alkyl}]_2$, wherein R^4, R^5 and R^{10} are as defined above, and

M is
1. a hydrogen atom,
2. $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
3. $-C(O)-NR^4R^5$,
4. $-(C_6-C_{14})$-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
5. $-(C_6-C_{14})$-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
6. a 5- to 7-membered cyclic group, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
7. a 5- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, wherein R^{14} is defined above.

8. A compound of formula I as claimed in one or more of claims 1 to 7, wherein

R^0 is phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R^2, or
pyridyl, wherein pyridyl is unsubstituted or mono-, disubstituted independently of one another by R^2,

R^2 is halogen or -CN,
Q is a direct bond
Q' is -O-,
X is $-(C_1-C_3)$-alkylen,
W is phenyl or pyridyl, wherein W is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

provided that Q' and U are not in an ortho position with respect to each other;

R^1 is halogen, $-NO_2$, -CN, $-NH_2$, (C_1-C_4)-alkylamino-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -OH, $-SO_2-NH_2$, (C_1-C_4)-alkyloxy-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, (C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, (C_1-C_4)-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, (C_1-C_4)-alkylsulfonyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, bis$[(C_1-C_4)\text{-alkyl}]$amino, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-C(O)-NH_2$, -C(O)-OH, $-C(O)-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-C(O)-NH-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-C(O)-NH-[(C_1-C_4)\text{-alkyl}]_2$, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-C(NH)-NH_2$, ureido, $-(C_1-C_4)$-alkylthio, wherein alkylthio is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, or $R^{11}R^{12}N$-, or

two R^1 residues bonded to adjacent ring carbon atoms together with the carbon atoms to which they are bonded form an aromatic ring condensed to W, where the ring formed by the two R^1 residues is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

R^{11} and R^{12} together with the nitrogen atom to which they are bonded form a saturated or unsaturated 5- to 6-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^{11} and R^{12} can contain one or two identical or different ring heteroatoms chosen from oxygen or nitrogen,

R^{13} is halogen, -CN, $-(C_1-C_4)$-alkyl, $-(C_1-C_4)$-alkyloxy, $-CF_3$, $-C(O)-NH_2$ or $-NH_2$,

R^{10} is hydrogen atom or methyl,

U is $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n$, wherein n is zero, 1 or 2, m is zero or 1,

R^4 and R^5 are independently of one another identical or different and are hydrogen atom, $-(C_1-C_6)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-(C_6-C_{14})$-aryl-(C_1-C_4)-alkyl-, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, $-(C_6-C_{14})$-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-(C_6-C_{14})$-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} or $-(C_6-C_{14})$-heteroaryl-(C_1-C_4)-alkyl-, wherein alkyl and heteroaryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, or

R^4 and R^5 together with the nitrogen atom to which they are bonded form a saturated 5- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^4 and R^5 can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

G is a direct bond, $-(CH_2)_m$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n$, $-(CH_2)_m-C(O)-(CH_2)_n$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n$ or $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n$,
wherein n, m, and R^{10} are as defined above

V is
1. a 5- to 6-membered cyclic group, containing up to 1 or 2, heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
2. a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
3. a 6- to14-membered heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

R^{14} is halogen, -OH, $-NR^4R^5$, =O, $-(C_1-C_4)$-alkyl, $-(C_1-C_4)$-alkoxy, -C(O)-OH, -CN, $-C(O)-O-(C_1-C_4)$-alkyl, $-C(O)-NR^4R^5$, $-(C_1-C_8)$-alkylsulfonyl, $-C(O)-NH_2$, $-SO_2-NR^4R^5$, $-C(O)-NH-(C_1-C_8)$-alkyl, $-C(O)-NH-[(C_1-C_8)\text{-alkyl}]_2$, wherein R^4 or R^5 are as defined above, and

M is
1. a hydrogen atom,
2. $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
3. $-C(O)-NR^4R^5$,
4. $-(C_6-C_{14})$-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
5. $-(C_6-C_{14})$-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
6. a 5- to 6-membered cyclic group, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
7. a 5- to 6-membered cyclic group, containing up to 1 or 2 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, wherein R^{14} is defined above.

9. A compound of formula I as claimed in one or more of claims 1 to 8, wherein

R^0 is phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R^2, or
pyridyl, wherein pyridyl is unsubstituted or mono-, disubstituted independently of one another by R^2,

R^2 is chlorine,
Q is a direct bond
Q' is -O-,
X is ethylene,
W is phenyl or pyridyl, wherein W is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

provided that Q' and U are not in an ortho position with respect to each other;

R^1 is halogen, $-NO_2$, -CN, $-NH_2$, (C_1-C_4)-alkylamino-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, -OH, $-SO_2-NH_2$, (C_1-C_4)-alkyloxy-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, (C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, (C_1-C_4)-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, (C_1-C_4)-alkylsulfonyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, bis[(C_1-C_4)-alkyl]amino, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-C(O)-NH_2$, -C(O)-OH, $-C(O)-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-C(O)-NH-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-C(O)-NH-[(C_1-C_4)\text{-alkyl}]_2$, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-C(NH)-NH_2$, ureido, $-(C_1-C_4)$-alkylthio, wherein alkylthio is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, or $R^{11}R^{12}N$-, or

two R^1 residues bonded to adjacent ring carbon atoms together with the carbon atoms to which they are bonded form an aromatic ring condensed to W, where the ring formed by the two R^1 residues is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

R^{11} and R^{12} together with the nitrogen atom to which they are bonded form a saturated or unsaturated 5- to 6-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^{11} and R^{12} can contain one or two identical or different ring heteroatoms chosen from oxygen or nitrogen,

R^{13} is halogen, -CN, $-(C_1-C_4)$-alkyl, $-(C_1-C_4)$-alkyloxy, $-CF_3$, $-C(O)-NH_2$ or $-NH_2$,

R^{10} is hydrogen atom or methyl,

U is $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n$, wherein n is zero, 1 or 2, m is zero or 1,

R^4 and R^5 are independently of one another identical or different and are hydrogen atom, $-(C_1-C_6)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-(C_6-C_{14})$-aryl-(C_1-C_4)-alkyl-,

wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, $-(C_6-C_{14})$-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, $-(C_6-C_{14})$-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} or $-(C_6-C_{14})$-heteroaryl-(C_1-C_4)-alkyl-, wherein alkyl and heteroaryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13}, or

R^4 and R^5 together with the nitrogen atom to which they are bonded form a saturated 5- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^4 and R^5 can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

G is a direct bond, $-(CH_2)_m$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n$, $-(CH_2)_m-C(O)-(CH_2)_n$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n$,$-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n$ or $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n$, wherein n, m, and R^{10} are as defined above

V is
1. a 5- to 6-membered cyclic group, containing up to 1 or 2, heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
2. a 6-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
3. a 6-membered heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

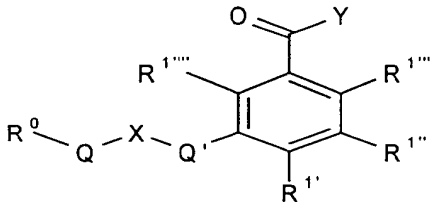
R^{14} is halogen, -OH, $-NR^4R^5$, =O, $-(C_1-C_4)$-alkyl, $-(C_1-C_4)$-alkoxy, -C(O)-OH, -CN, $-C(O)-O-(C_1-C_4)$-alkyl, $-C(O)-NR^4R^5$, $-(C_1-C_8)$-alkylsulfonyl, $-C(O)-NH_2$, $-SO_2-NR^4R^5$, $-C(O)-NH-(C_1-C_8)$-alkyl, $-C(O)-NH-[(C_1-C_8)\text{-alkyl}]_2$, wherein R^4 or R^5 are as defined above, and

M is
1. a hydrogen atom,
2. $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
3. $-C(O)-NR^4R^5$,
4. $-(C_6-C_{14})$-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
5. $-(C_6-C_{14})$-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted inde-

pendently of one another by R^{14},
6. a 5- to 6-membered cyclic group, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
7. a 5- to 6-membered cyclic group, containing up to 1 or 2 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, wherein R^{14} is defined above.

10. A process for the preparation of a compound of the formula I as claimed in one or more of claims 1 to 9, which comprises

a) wherein W is phenyl and U is $-(CH_2)_0-C(O)NR^{10}-(CH_2)_1-$, linking a compound of the formula XI,



XI

wherein R^0, Q, Q' and X are as defined in claims 1 to 9, or functional groups of the formula XI are precursor groups or are protected by protective groups, $R^{1'}$, $R^{1'''}$, $R^{1''''}$ and $R^{1'''''}$ are independently from each other hydrogen atom, R^1, which is as defined in formula I, precursor groups or can be protected by protective groups, and Y is a nucleophilically substituable leaving group or a hydroxyl group, which may also be attached to a polystyrene resin,
with a compound of the formula XII

$$\mathbf{H\text{-}NR^{10}\text{-}V\text{-}G\text{-}M} \qquad \text{(XII)}$$

wherein R^{10}, V, G and M are as defined in claims 1 to 9 or functional groups of the formula XII are precursor groups or protected by protective groups, or
b) reacting a compound of the formula XII with a compound of the formula XIII

$$R^0\text{-}Q\text{-}X\text{-}Q'\text{-}W\text{-}C(O)\text{-}Y \qquad \text{(XIII)}$$

wherein R^0, Q, Q', X, W and Y are as defined in claims 1 to 9 or functional groups of the formula XIII are precursor groups or are protected by protective groups, and Y is a nucleophilically leaving group or a hydroxyl group, which may also be attached to a polystyrene resin.

11. A pharmaceutical preparation, comprising at least one compound of the formula I as claimed in one or more of claims 1 to 9 and/or its physiologically tolerable salts and a pharmaceutically acceptable carrier.

12. The use of a compound of the formula I as claimed in one or more of claims 1 to 9 and/or their physiologically tolerable salts and/or their prodrugs for the production of pharmaceuticals for inhibition of factor Xa and/or factor VIIa or for influencing blood coagulation or fibrinolysis.

13. The use as claimed in claim 12 for influencing blood coagulation, inflammatory response, fibrinolysis, cardiovascular disorders, thromboembolic diseases, restenoses, abnormal thrombus formation, acute myocardial infarction, unstable angina, acute vessel closure associated with thrombolytic therapy, thromboembolism, percutaneous, pathologic thrombus formation occuring in the veins of the lower extremities following abdominal, knee and hip surgery, transluminal coronary angioplasty, transient ischemic attacks, stroke, disseminated systemic intravascular coagulatopathy ocurring in vascular systems during septic shock, a risk of pulmonary thromboembolism, certain viral infections or cancer, intravascular coagulatopathy ocurring in vascular systems during septic shock, coronary heart disease, myocardial infarction, angina pectoris, vascular restenosis, for example restenosis following angi-

oplasty like PTCA, adult respiratory disstress syndrome, multi-organ failure, stroke and disseminated intravascular clotting disorder, thromboses like deep vein and proximal vein thrombosis which can occur following surgery.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 00 12 8477

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	HANESSIAN S S ET AL: "Exploring the chiral space within the active site of alpha-thrombin with a constrained mimic of d-Phe-Pro-Arg - design, synthesis, inhibitory activity, and X-ray structure of an enzyme-inhibitor complex" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 10, no. 3, February 2000 (2000-02), pages 243-247, XP004188826 ISSN: 0960-894X *Scheme 3* * abstract; examples 18-21 * --- -/--	1-13	C07D401/00 C07D213/30 C07D333/16 C07D333/58 A61K31/38 A61K31/435

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

C07D
A61K

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
MUNICH	28 November 2001	Härtinger, S

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

European Patent Office

INCOMPLETE SEARCH
SHEET C

Application Number
EP 00 12 8477

Claim(s) searched incompletely:
1-13

Reason for the limitation of the search:

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 84 EPC). For these reasons, a meaningful search over the whole breadth of the claims is impossible, and consequently, the search has been restricted.

Moreover, the present claims relate to an extremely large number of possible compound classes, ranging from peptides (eg. R QXQ'W = phe-pro) to nonpeptides, and from natural products (eg. QXQ'W = O-glucose) to synthetic compound classes. Support within the meaning of Article 84 EPC and disclosure within the meaning of Article 83 EPC is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed.

However, with reference to the fact that the application lacks unity of invention, only those parts relating to the compounds prepared in the examples and closely related homologous compounds have been searched, which belong to the first group of inventions named in the annex to this search report. Within this already restricted group, the initial phase of the search revealed again a very large number of documents relevant to the issue of novelty. So many documents were retrieved even for the first mentioned group of inventions that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 84 EPC). For these reasons, a meaningful search over the whole breadth of the alternatives belonging to the first group of inventions is impossible, and consequently, the search has been restricted to compounds of the Formula (I), where R is selected from phenyl or pyridyl; -QXQ'- is an alkylene-oxygen linker; W is selected from phenyl and pyridyl.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 00 12 8477

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	HOEKSTRA ET AL: "Potent, Orally Active GPIIb/IIIa Antagonists Containing a Nipecotic Acid Subunit. Structure-Activity Studies Leading to the Discovery of RWJ-53308" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 42, no. 25, 1999, pages 5254-5265, XP002142349 ISSN: 0022-2623 * page 5254, left-hand column; examples 2,3; table 2 * ---	1-13	
X	CAMPILLO N ET AL: "Novel Arylpyrazino[2,3-c][1,2,6]thiadiazine 2,2-Dioxides as Platelet Aggregation Inhibitors. 2." JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 42, 1999, pages 3279-3288, XP002181373 ISSN: 0022-2623 * table 1 * ---	1-13	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	WALSER A ET AL: "TRIAZOLOBENZO- AND TRIAZOLOTHIENODIAZEPINES AS POTENT ANTAGONISTS OF PLATELET ACTIVATING FACTOR" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 34, no. 3, 1991, pages 1209-1221, XP000942214 ISSN: 0022-2623 * example 1; tables * --- -/--	1-13	

EPO FORM 1503 03.82 (P04C10)

European Patent Office

LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 00 12 8477

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims: 1(part)-13(part)

   compounds (I) of the type R -alkylene-O-W-UVGM

2. Claims: 1(part)-13(part)

   compounds (I) of the type R -W-UVGM

3. Claims: 1(part)-13(part)

   compounds (I) of the type R -CO-W-UVGM

4. Claims: 1(part)-13(part)

   compounds (I) of the type R -SO2-W-UVGM

5. Claims: 1(part)-13(part)

   compounds (I) of the type R -SO2NH-alkylene-W-UVGM

6. Claims: 1(part)-13(part)

   compounds (I) of the type R -CONH-W-UVGM

7. Claims: 1(part)-13(part)

   compounds (I) of the type R -O-W-UVGM

8. Claims: 1(part)-13(part)

   compounds (I) of the type R -alkylenen-W-UVGM

9. Claims: 1(part)-13(part)

   compounds (I) of the type R -alkylene-NHCO-W-UVGM

10. Claims: 1(part)-13(part)

    peptide compounds (I) having W = prolyl

11. Claims: 1(part)-13(part)

European Patent Office

LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 00 12 8477

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

compounds (I) wherein QXQ' is different from above groups

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 00 12 8477

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	DATABASE CROSSFIRE BEILSTEIN [Online] BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT, DE; BRN 146145, XP002181378 * abstract * -& REHSE K ET AL: "New NO Donors with Antithrombotic and Vasodilating Activities, Part 27" [Online] 14 June 2000 (2000-06-14) XP002181377 Retrieved from the Internet: <URL: www3.interscience.wiley.com/cgi-bin/abstract/72507169/START> [retrieved on 2001-10-26] ---	1-13	
X	DATABASE CROSSFIRE BEILSTEIN [Online] BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT, DE; BRN 8523212, XP002181379 * abstract * ---	1-13	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	DATABASE CROSSFIRE BEILSTEIN [Online] BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT, DE; BRN 4301943, XP002181380 * abstract * --- -/--	1-13	

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 00 12 8477

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y	CHOI-SLEDESKI Y M ET AL: "Aminoisoquinolines: Design and Synthesis of an Orally Active Benzamidine Isostere for the Inhibition of Factor XA" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 17, 6 September 1999 (1999-09-06), pages 2539-2544, XP004188859 ISSN: 0960-894X * page 2540, line 1 - line 9; table 1 * ---	1-13	
X	MAIGNAN S J ET AL: "Crystal STructures of Human Factor Xa Complexed with Potent Inhibitors" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 43, 24 August 2000 (2000-08-24), pages 3226-3232, XP002181374 ISSN: 0022-2623 * table 1 * ---	1-13	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	DATABASE CROSSFIRE BEILSTEIN [Online] BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT, DE; BRN 95671, XP002181381 * abstract * ---	1-13	
X	DATABASE CROSSFIRE BEILSTEIN [Online] BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT, DE; BRN 8639815, XP002181382 * abstract * --- -/--	1-13	

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 00 12 8477

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y	HE W ET AL: "Nonbenzamidine compounds as selective factor xa inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 10, no. 15, 7 August 2000 (2000-08-07), pages 1737-1739, XP004213235 ISSN: 0960-894X * table 1 * ---	1-13	
X	OGINO T ET AL: "Discovery of FR115092: a novel antinephritic agent" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 1-6, 6 January 1998 (1998-01-06), pages 75-80, XP004136626 ISSN: 0960-894X * table 1 * ---	1-13	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	DATABASE CROSSFIRE BEILSTEIN [Online] BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT, DE; BRN 7813412, XP002181383 * abstract * ---	1-13	
X	DATABASE CROSSFIRE BEILSTEIN [Online] BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT, DE; BRN 8658351, XP002181384 * abstract * --- -/--	1-13	

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 00 12 8477

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	DATABASE CROSSFIRE BEILSTEIN [Online] BEILSTEIN INSTITUT ZUR FOEDERUNG DER WISSENSCHAFTEN, FRANKFURT, DE; BRN 1430606, XP002181385 * abstract * ---	1-13	
X	DATABASE CROSSFIRE BEILSTEIN [Online] BEILSTEIN INSTITUT ZUR FOEDERUNG DER WISSENSCHAFTEN, FRANKFURT, DE; BRN 3069936, XP002181386 * abstract * ---	1-13	
Y	PITTS W J ET AL: "Isoxazolines as Potent Antagonists of the Integrin alpha v betha 3" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 43, 2000, pages 27-40, XP002181375 ISSN: 0022-2623 * figure 2; examples 3,15; table 1 * ---	1-13	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	HERRON D K ET AL: "1,2-Dibenzamidobenzene Inhibitors of Human Factor Xa" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 43, 9 March 2000 (2000-03-09), pages 859-872, XP002181376 ISSN: 0022-2623 * figure 1; examples 1-10; table 1 * --- -/--	1-13	

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 00 12 8477

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	FUJIO M ET AL: "N-[1-(2-Phenylethyl)pyrrolidin-3-yl]-1-adamantanecarboxamides as novel 5-HT2 receptor antagonists" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 10, no. 21, 6 November 2000 (2000-11-06), pages 2457-2461, XP004224239 ISSN: 0960-894X * table 1 * ---	1-13	
X	EP 0 019 589 A (PENTAPHARM AG) 26 November 1980 (1980-11-26) * example 29 * ---	1-13	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	BAILEY P D ET AL: "How to make Drugs Orally Available" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, VERLAG CHEMIE. WEINHEIM, DE, vol. 39, no. 3, 4 February 2000 (2000-02-04), pages 506-508, XP002184168 ISSN: 0570-0833 * example 4; table 1 * ---	1-13	
X	DATABASE CROSSFIRE BEILSTEIN [Online] BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT, DE; BRN 8665019, XP002181387 * abstract * --- -/--	1-13	

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 00 12 8477

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	OKADA Y ET AL: "Development of plasmin and plasma kallikrein selective inhibitors and their effect on M1 (melanoma) and ht29 cell lines" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 10, no. 19, 2 October 2000 (2000-10-02), pages 2217-2221, XP004212007 ISSN: 0960-894X * table 2 * ---	1-13	
X	DATABASE CROSSFIRE BEILSTEIN [Online] BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT, DE; BRN 8360262, XP002181446 * abstract * ---	1-13	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	DATABASE CROSSFIRE BEILSTEIN [Online] BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT, DE; BRN 8564005, XP002181447 * abstract * ---	1-13	
Y	ROUSSEL P ET AL: "Inhibition of the Tissue Factor/Factor VIIa Complex - Lead Optimisation Using Combinatorial Chemistry" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 55, no. 19, 7 May 1999 (1999-05-07), pages 6219-6230, XP004164552 ISSN: 0040-4020 * figure 2 * --- -/--	1-13	

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 00 12 8477

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y	DATABASE CROSSFIRE BEILSTEIN [Online] BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT, DE; BRN 8511019, XP002181448 * abstract * ---	1-13	
X	GB 2 011 892 A (SUMITOMO CHEMICAL CO) 18 July 1979 (1979-07-18) * table 1 * ---	1-10	
X	US 4 309 212 A (TAKEMOTO ICHIKI ET AL) 5 January 1982 (1982-01-05) * tables * ---	1-10	
X	DATABASE CROSSFIRE BEILSTEIN [Online] BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT, DE; BRN 869622, XP002181449 * abstract * ---	1-11	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	DATABASE CROSSFIRE BEILSTEIN [Online] BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT, DE; BRN 7062387, XP002181450 * abstract * ---	1-10	
X	DATABASE CROSSFIRE BEILSTEIN [Online] BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT, DE; BRN 8653610, XP002181451 * abstract * --- -/--	1-11	

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 00 12 8477

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	DATABASE CROSSFIRE BEILSTEIN [Online] BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT, DE; BRN 8326226, XP002181452 * abstract * ---	1-11	
X	DATABASE CROSSFIRE BEILSTEIN [Online] BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT, DE; BRN 8331996, XP002181453 * abstract * -----	1-11	
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)

EPO FORM 1503 03.82 (P04C10)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 00 12 8477

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

28-11-2001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0019589 A	26-11-1980	AT 5254 T	15-11-1983
		AU 547872 B2	07-11-1985
		AU 5990480 A	03-12-1980
		CA 1161431 A1	31-01-1984
		WO 8002559 A1	27-11-1980
		DE 3065506 D1	15-12-1983
		DK 155781 A ,B,	07-11-1981
		DK 509788 A ,B,	13-09-1988
		EP 0019589 A1	26-11-1980
		ES 491376 D0	16-05-1981
		ES 8105865 A1	01-09-1981
		JP 1616944 C	30-08-1991
		JP 2044839 B	05-10-1990
		JP 62294695 A	22-12-1987
		JP 1616945 C	30-08-1991
		JP 2044840 B	05-10-1990
		JP 62294696 A	22-12-1987
		JP 1616946 C	30-08-1991
		JP 2044518 B	04-10-1990
		JP 62296899 A	24-12-1987
		JP 1450372 C	11-07-1988
		JP 57002253 A	07-01-1982
		JP 62057197 B	30-11-1987
		NO 811510 A ,B,	09-11-1981
		IL 60000 A	30-12-1983
		ZA 8002779 A	24-06-1981
GB 2011892 A	18-07-1979	JP 54088231 A	13-07-1979
		DE 2855699 A1	28-06-1979
		FR 2412520 A1	20-07-1979
		IT 1102412 B	07-10-1985
		PL 212041 A1	25-02-1980
US 4309212 A	05-01-1982	JP 1349455 C	28-11-1986
		JP 54115347 A	07-09-1979
		JP 61013704 B	15-04-1986
		JP 54117436 A	12-09-1979
		JP 1303744 C	28-02-1986
		JP 54079249 A	25-06-1979
		JP 60030307 B	16-07-1985
		AR 229391 A1	15-08-1983
		AU 522936 B2	01-07-1982
		AU 4105878 A	01-05-1980
		BG 33731 A3	15-04-1983
		BR 7807054 A	10-07-1979
		CA 1108184 A1	01-09-1981

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 00 12 8477

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

28-11-2001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4309212 A		CH 641770 A5	15-03-1984
		CS 201516 B2	28-11-1980
		DD 139711 A5	16-01-1980
		DE 2846723 A1	03-05-1979
		DK 478078 A	27-04-1979
		ES 474581 A1	16-01-1980
		ES 480717 A1	16-08-1980
		ES 480718 A1	16-01-1980
		FR 2407201 A1	25-05-1979
		GB 2010244 A ,B	27-06-1979
		HU 177145 B	28-07-1981
		IT 1160892 B	11-03-1987
		MX 5191 E	21-04-1983
		NL 7810700 A	01-05-1979
		PL 210522 A1	11-02-1980
		US 4690709 A	01-09-1987
		YU 250478 A1	30-04-1983
		BE 871562 A1	26-04-1979
		ZA 7806041 A	31-10-1979

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82